University of Alberta

Total Synthesis of (±)-Ceratopicanol, and Synthetic Studies Towards New Methods For Making Amides

by

Steven R. Magnuson

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A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY

Department of Chemistry

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled TOTAL SYNTHESIS OF (±)-CERATOPICANOL, AND SYNTHETIC STUDIES TOWARDS NEW METHODS FOR MAKING AMIDES submitted by STEVEN R. MAGNUSON in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

Dr. D. L. J. Clive

Dr. M. Cowie

Dr. H. J. Liu

Dr. P. Sporns

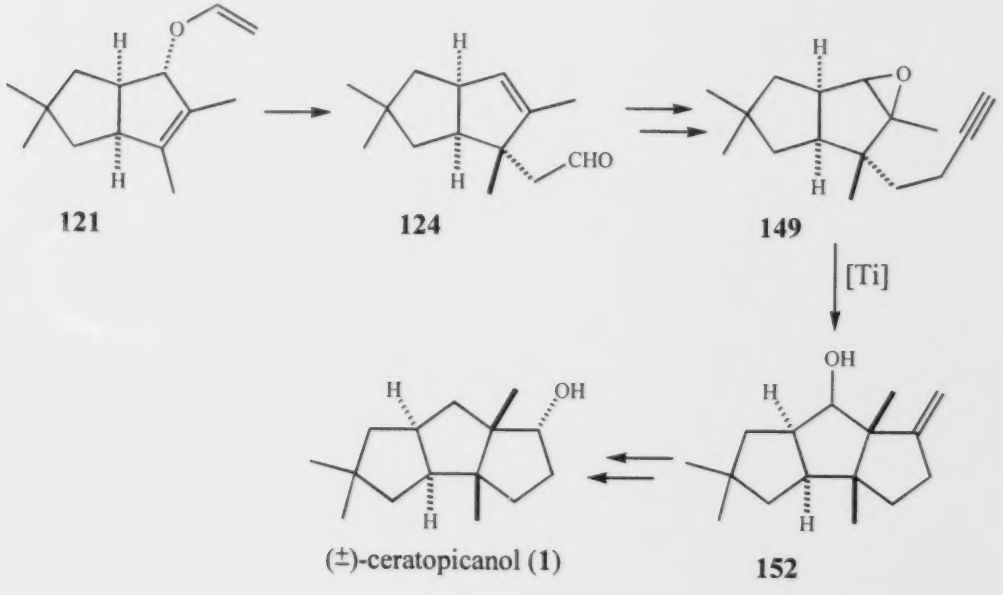
Dr. J. C. Vederas

Dr. R. G. A. Rodrigo
(external examiner)

To my family and friends

ABSTRACT

The first chapter of this thesis describes a synthesis of the linear triquinnane, ceratopicanol [(±)-**1**]. The route was based upon Claisen rearrangement (**121**→**124**) and radical cyclization (**149**→**152**), the radical being generated by titanium-induced opening of an epoxide.

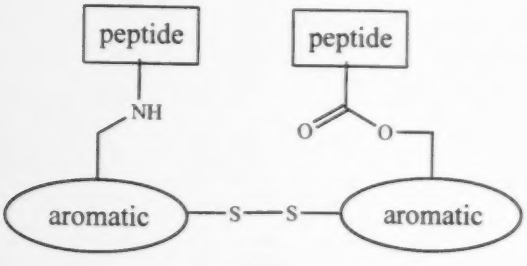


121 **124** **149** **152**

(±)-ceratopicanol (**1**)

The second chapter details our attempts at finding methods, that involve intramolecular *O*→*N* acyl transfer, for coupling peptide fragments. The first of the two approaches we considered — the disulfide approach — involved attempts at the synthesis of mixed disulfides (*cf.* **103**) which bring the amino terminus of one peptide chain into close proximity

with the carboxyl terminus of a second peptide chain, so that once the disulfide is formed, intramolecular peptide bond formation can occur. The second approach — the single template approach — involved attempts at joining the carboxyl terminus of one peptide chain, and the amino terminus of a second peptide chain to a template (*cf.* **98**). The amino terminus is joined to the template as an imine. Reduction of the imine could then be followed by intramolecular peptide bond formation.



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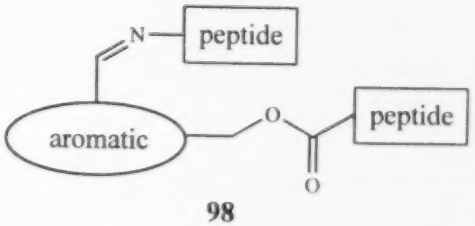

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List of Acronyms

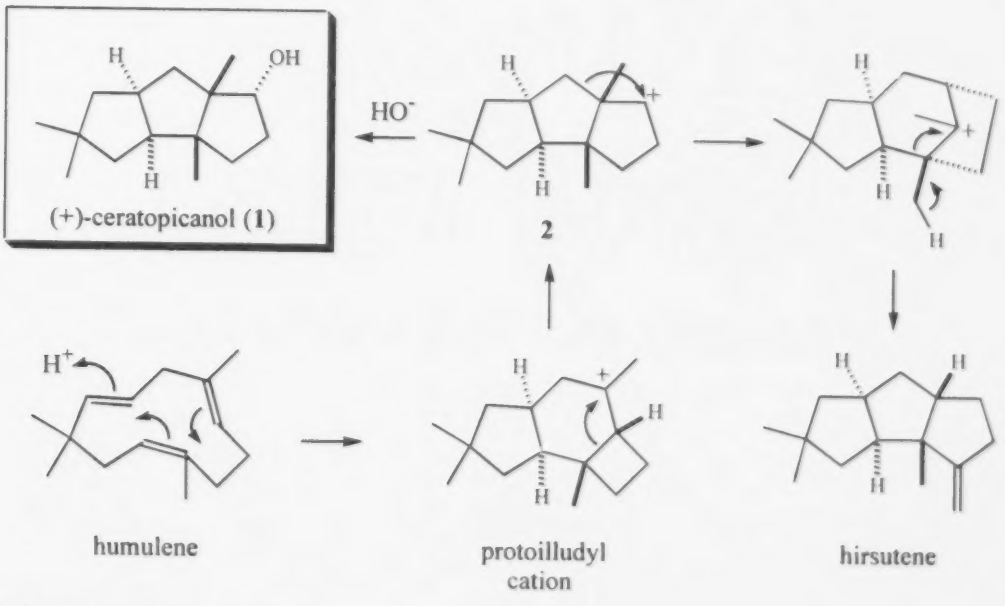
Ac	acetyl
AIBN	2,2-'azobisisobutyronitrile
BHT	2,6-di-^{t}butyl-4-methylphenyl
Boc	*t*-butoxycarbonyl
CAN	ceric ammonium nitrate
CBz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethoxycarbonyl
HMPA	hexamethylphosphoramide
LAH	lithium aluminum hydride
MCPBA	*m*-chloroperoxybenzoic acid
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate

PTSA	*p*-toluenesulfonic acid
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TRIBAL	triisobutylaluminum

CHAPTER I

Introduction - Triquinnane Synthesis:

Ceratopicanol (**1**) is a linear triquinnane sesquiterpene that was first reported[1] by Abraham and Hansen in 1988. The isolation of this natural product is of interest in the context of biogenetic theory, as the structure represents evidence for the generation *in vivo* of carbonium ion **2**, a species suggested[2] as an intermediate en route from humulene to hirsutene and related natural products (Scheme 1).[3]



Scheme 1

Sesquiterpenes is the name used to represent the broad range of C_{15} structures derived from farnesyl CoA in the terpenoid biosynthetic pathway.[4,3b] This class of compounds has over 50 different skeletal frameworks with new structures being isolated every year. Two of these skeletal types—the linear triquinnane (**3**) and the angular triquinnane (**4**)—are shown in Scheme 2.

3

4

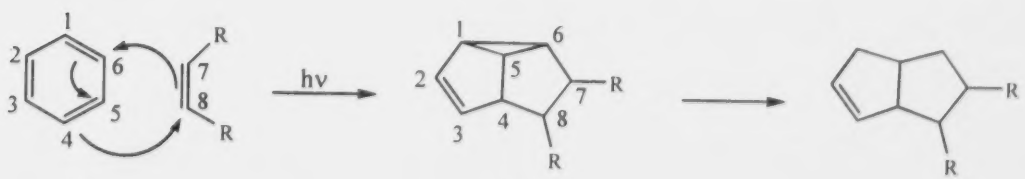
Scheme 2

Over the last 20 years the natural products based on these two skeletal sub-classes have received an incredible amount of synthetic attention.[5] Not surprisingly, a number of innovative and impressive methods for making fused 5-membered ring compounds have been developed, and the review section of this chapter will examine some of the more important methods used in natural product synthesis. An exhaustive and comprehensive evaluation of all triquinnane syntheses is well beyond the scope of this review, but a study of some of the techniques used will illustrate the wide range of interesting chemistry that has originated in this field.

A. Triquinnane Syntheses Based on Cycloadditions

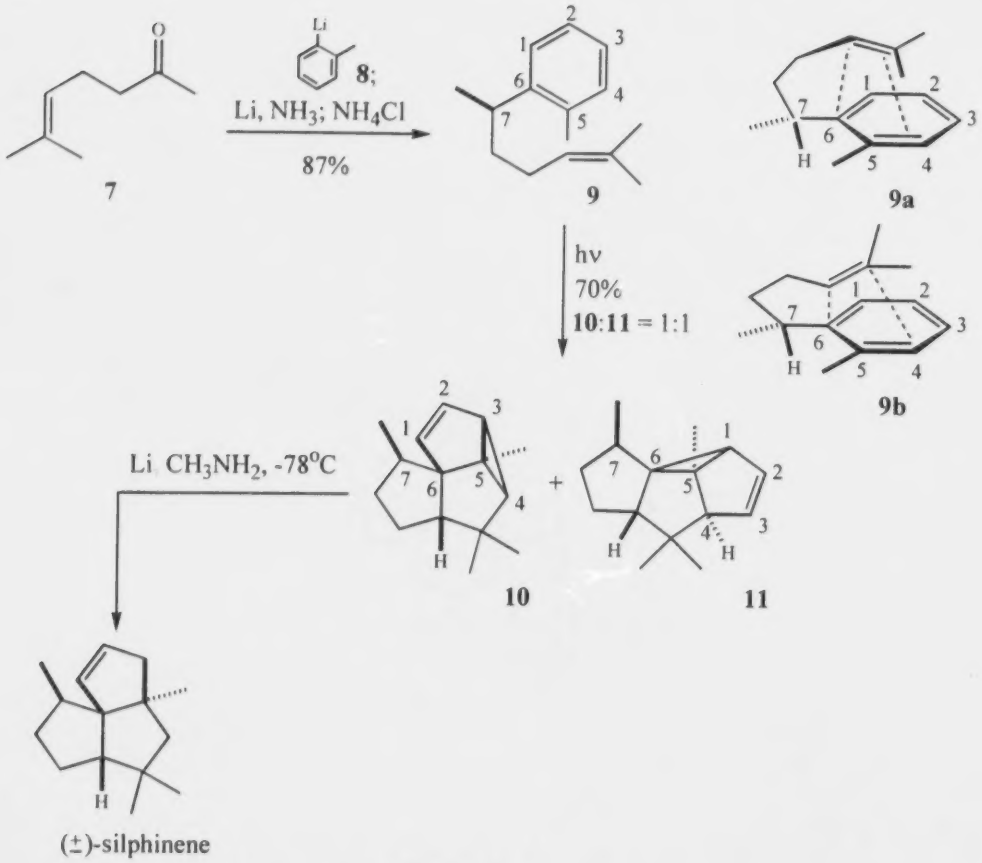
A large number of triquinnane syntheses have used cycloaddition reactions such as the arene-olefin cycloaddition, the Diels-Alder reaction, or a [2+2] cycloaddition in key ring forming steps.

i. Use of the Arene-Olefin Cycloaddition: Without much doubt, some of the most elegant triquinnane syntheses involve the *meta*-photoaddition of an olefin to an arene. This powerful method, first reported in the late 1960's,[6] has been studied extensively and applied to a number of efficient natural product syntheses by the Wender group.[7] As the name implies, the reaction involves addition of an olefin to *meta* positions of an arene ring, and this is achieved under photolysis conditions (Scheme 3). The resulting product is the tricycle **5**, which, after cyclopropane bond cleavage, gives rise to diquinnane **6**. Wender has applied the reaction *intramolecularly*[8] in a number of triquinnane syntheses.[9,10]



5 **6**

Scheme 3



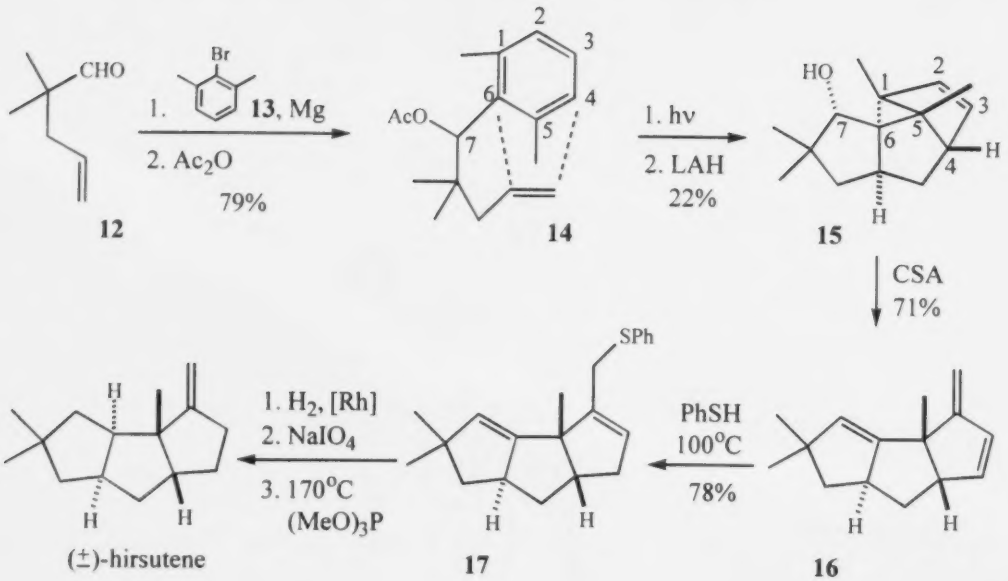
Scheme 4

One example that illustrates the efficiency of this reaction is Wender's three-step total synthesis of (±)-silphinene (Scheme 4).[9a] Commercially available ketone **7** was condensed with anion **8**, and the resulting alkoxide was reduced *in situ* to give arene-olefin **9**. Irradiation of **9** induced cycloaddition and regioisomers **10** and **11** were formed in a 1:1 ratio. The stereochemical outcome of the processes was explained by considering conformation **9a**, in which the

methyl group on C(7) is orientated away from the methyl group on the arene ring, thus minimizing steric congestion. The *exo* orientation in **9a**, required for the formation of **10** and **11**, is attributable to the better overlap between the reacting *pi* and arene centers relative to the so-called *endo* analog (**9b**). This second conformation (**9b**) also has the C(7) and C(5) methyl groups orientated away from one another, but overlap between the pi and arene orbitals is less favorable. The third and final step of the synthesis required regioselective reductive cleavage of the cyclopropane ring along the C(3)-C(4) bond in **10**. Treatment with lithium in methylamine at low temperature resulted in the desired cleavage giving, after purification, (±)-silphinene.

Wender has also used the arene-olefin *meta*-photocycloaddition to synthesize the angular triquinnanes (±)-subergorgic acid,[9b] (±)-silphiperfol-6-ene,[9c] (±)-7αH-silphiperfol-5-ene,[9c] (±)-7βH-silphiperfol-5-ene,[9c] and (±)-isocomene.[9d] Each of these syntheses required the construction of suitable cycloaddition precursors, as well as several manipulations following cycloaddition, but all were characterized by the remarkably efficient construction of the triquinnane framework.

When one considers the cycloaddition that is involved in the conversion **9→11** (Scheme 4), it is clear that the



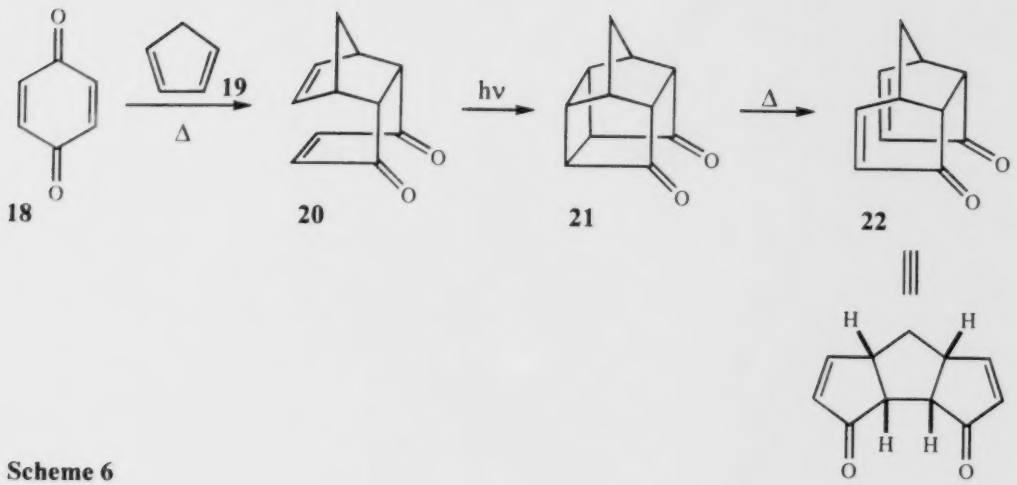
Scheme 5

arene-olefin *meta*-cycloaddition may also be used in linear triquinnane syntheses,[10] and one example is Wender's synthesis of hirsutene (Scheme 5).[10a] The cycloaddition precursor **14** was made by Grignard reaction of xylene **13** with aldehyde **12**, followed by alkoxide capture, using acetic anhydride. Photolysis of **14** then gave cycloadduct **15**, after deacetylation. Three other separable isomers were also formed, but in lesser amounts. The critical cyclopropane bond cleavage between C(1) and C(6) was accomplished by acid catalyzed dehydration (**15→16**). With the triquinnane framework now constructed, the synthesis was completed by first temporarily protecting the *exo* methylene substituent, using 1,4-free radical addition of thiophenol to the diene

moiety (**16**→**17**). The remaining double bonds were then reduced, and the exo methylene was regenerated by oxidizing the sulfide to the corresponding sulfoxide, which underwent β-elimination.

ii. Use of the Diels-Alder Reaction: One conspicuous feature of the arene-olefin cycloaddition is the efficiency with which the triquinnane framework can be constructed, but a noteworthy consequence of using the reaction is the lack of regioselectivity. Mixtures of regioisomers are usually formed during the photoaddition, and separation is often troublesome. It is not surprising therefore, that the Diels-Alder reaction—which is well-known for its high regioselectivity—has also been used in a number of triquinnane syntheses.[11] After cycloaddition, the desired five-membered ring of the triquinnane framework can then be formed using a suitable contraction or rearrangement of the initial six-membered ring.

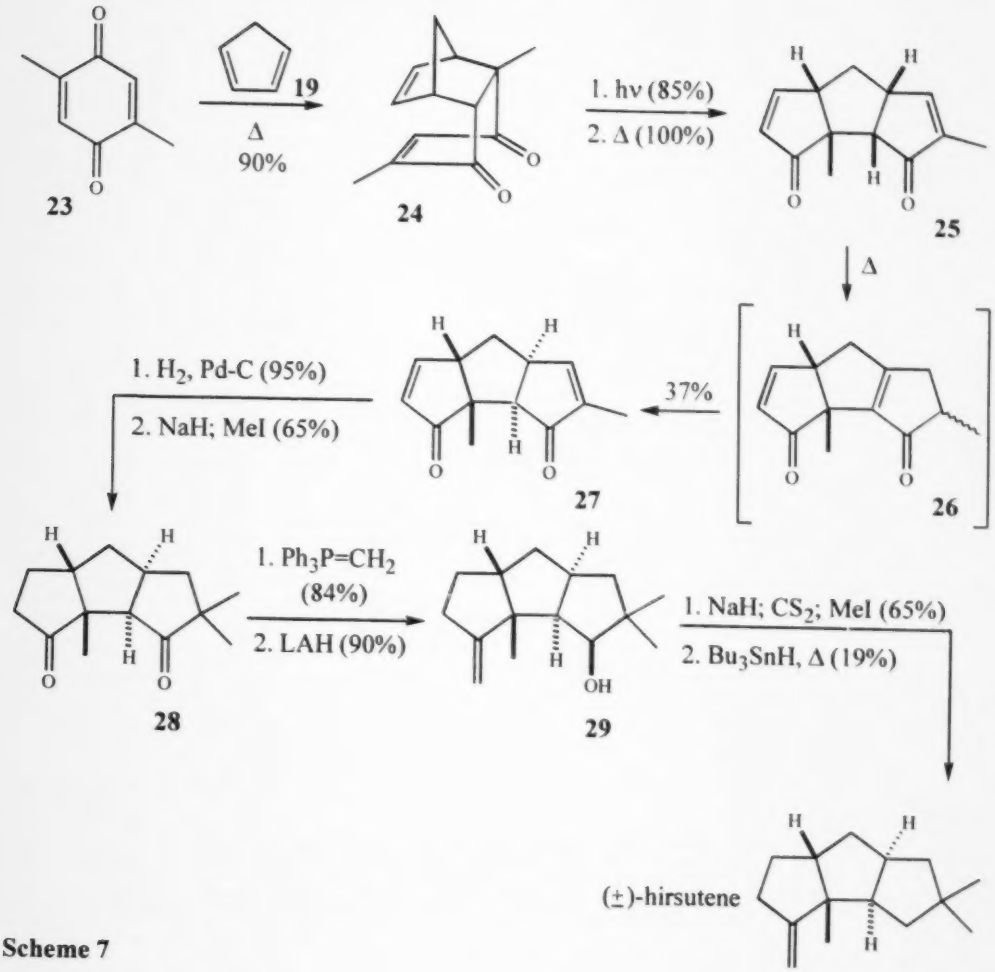
Mehta has employed the Diels-Alder reaction in a general protocol for the synthesis of linear triquinnanes (Scheme 6).[12] Thus, diene **19** and dienophile **18** gave the expected adduct **20**, which undergoes [2+2] photoaddition to Cookson's caged dione[13] **21**. Mehta recognized[14] that **21** was an immediate precursor to triquinnane **22**, since thermally



Scheme 6

induced cyclobutane fragmentation would give the desired compound.

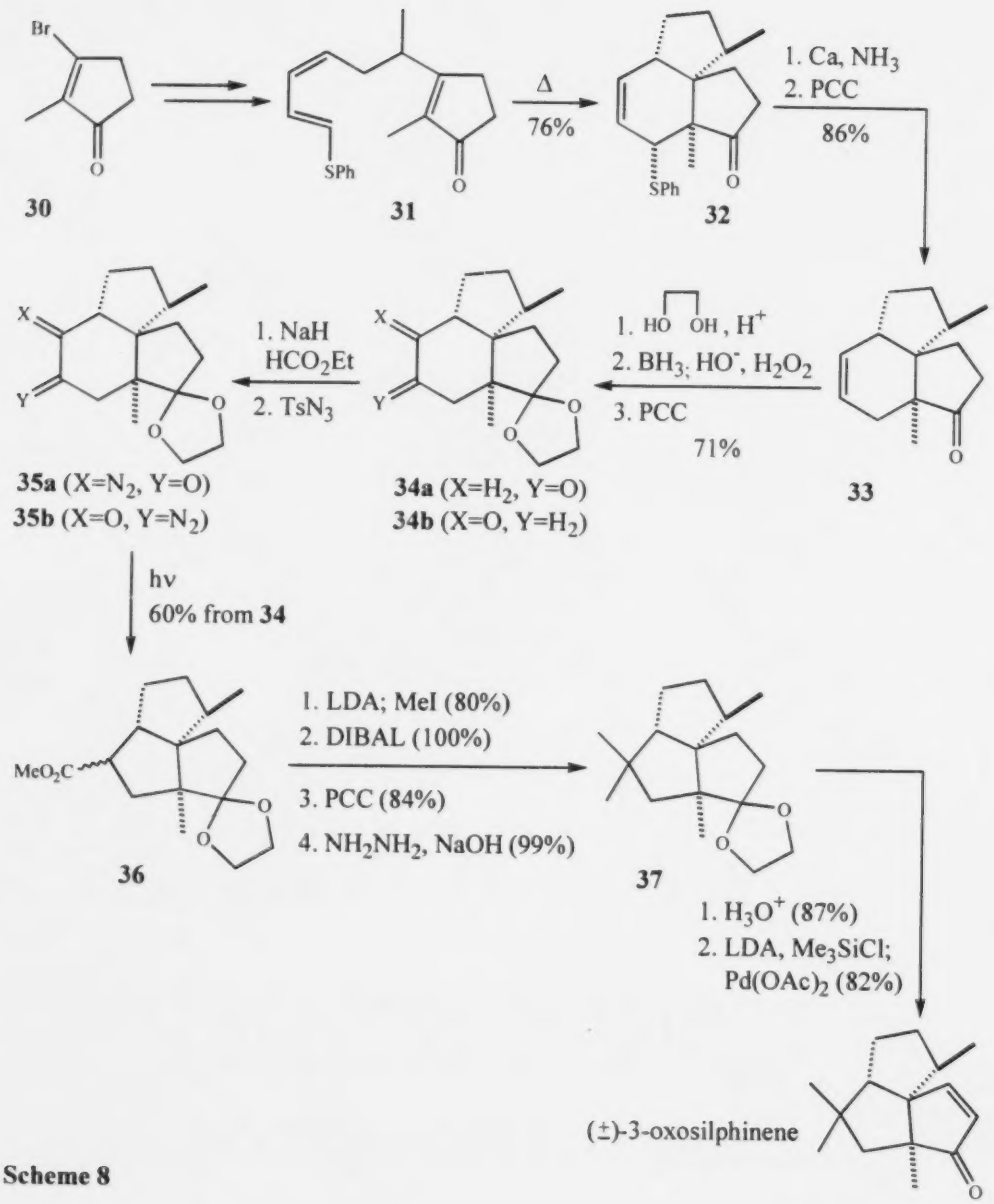
Mehta has illustrated this elegant idea in a synthesis of hirsutene (Scheme 7).[12] Diene **19** and dienophile **23** underwent Diels-Alder reaction to form adduct **24**. Cyclobutane formation and regioselective fragmentation then afforded *cis-syn-cis*-triquinnane **25**. At this point, it was necessary to invert the stereochemistry at one of the ring junctions so as to arrive at the *cis-anti-cis*-triquinnane **27**. Whereas base-mediated and metal-catalyzed procedures were not successful, thermal isomerization, through bis(enone) **26**, provided access to **27**, although in modest yield. Reduction of the double bonds and regioselective methylation then furnished dione **28**, and Wittig reaction at the less hindered carbonyl, followed by reduction of the



Scheme 7

remaining ketone gave alcohol **29**. Lastly, Barton deoxygenation afforded (±)-hirsutene.

Ihara and co-workers have also used a Diels-Alder reaction in their syntheses of the linear triquinnane (±)-$\Delta^{9(12)}$-capnellene[15] and the angular triquinnane (±)-3-oxosilphinene.[16] In the synthesis of the latter (Scheme 8), the Diels-Alder precursor **31** was constructed in three steps

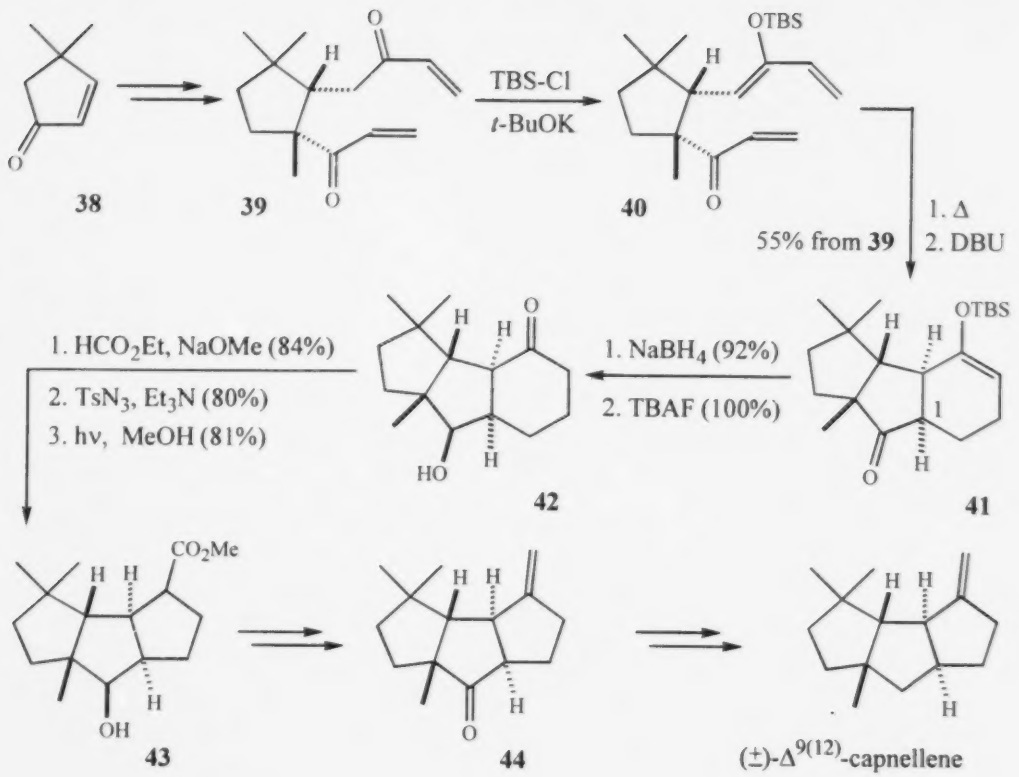


Scheme 8

from bromide **30**. Intramolecular cycloaddition of **31** then proceeded smoothly giving tricyclic ketone **32** as the sole product. The phenylthio group was removed by dissolving metal reduction, during which the carbonyl was also reduced.

Oxidation of the resulting alcohol afforded ketone **33**, and it was now necessary to contract the six-membered ring to the required cyclopentane. This was accomplished by Wolff rearrangement. To prepare for the rearrangement, the carbonyl of **33** was first protected, and hydroboration-oxidation led to a 3:2 mixture of ketones **34a** and **34b**. Formylation, followed by diazo transfer, gave diazo ketones **35a** and **35b**. At this stage, irradiation-induced rearrangement furnished the angular triquinnane **36**. With the desired framework now in hand, the synthesis was completed by building up the *gem*-dimethyl group (**36**→**37**), deprotecting the ketone, and introducing the double bond.

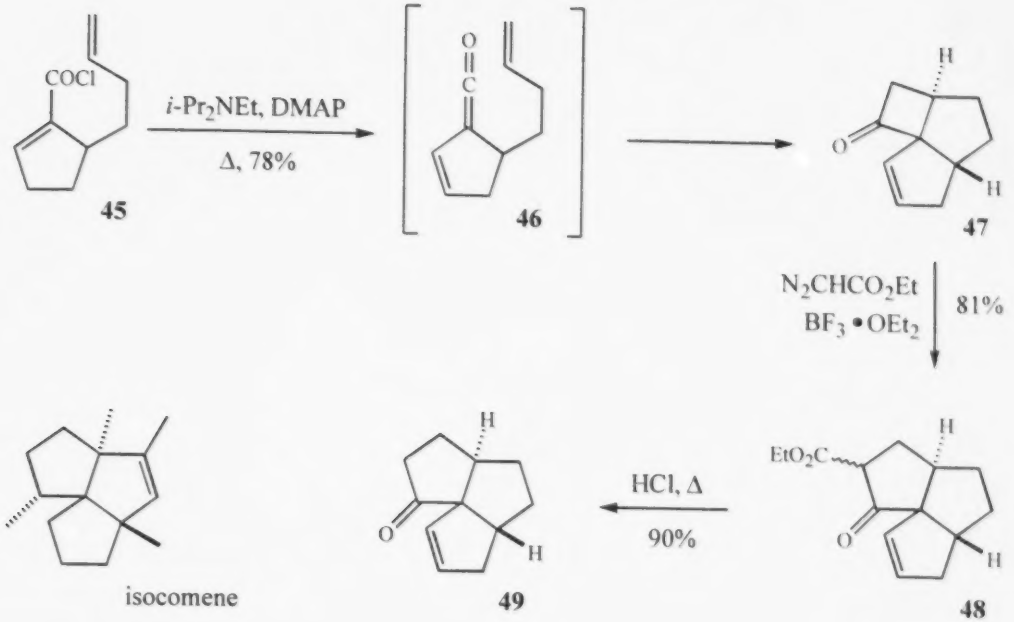
Ihara's synthesis of (±)-$\Delta^{9(12)}$-capnellene[15] (Scheme 9) began with enone **38**. This was first transformed into bis(enone) **39**, which was itself converted into the silyl enol ether **40**. The latter underwent intramolecular Diels-Alder reaction, and ketone **41** was obtained as the sole product after epimerization at C(1). Reduction and desilylation afforded ketone **42**, and then the key ring contraction (**42**→**43**) was again accomplished by Wolff rearrangement. Triquinnane **43** was elaborated in a number of steps into ketone **44**, which was an intermediate in an earlier synthesis of (±)-$\Delta^{9(12)}$-capnellene.[17]



Scheme 9

iii. Use of [2+2] Cycloaddition: In the preceding section, Diels-Alder reaction followed by ring *contraction* was used to build the triquinnane system. In an analogous way, [2+2] cycloaddition followed by ring *expansion* can serve the same purpose.

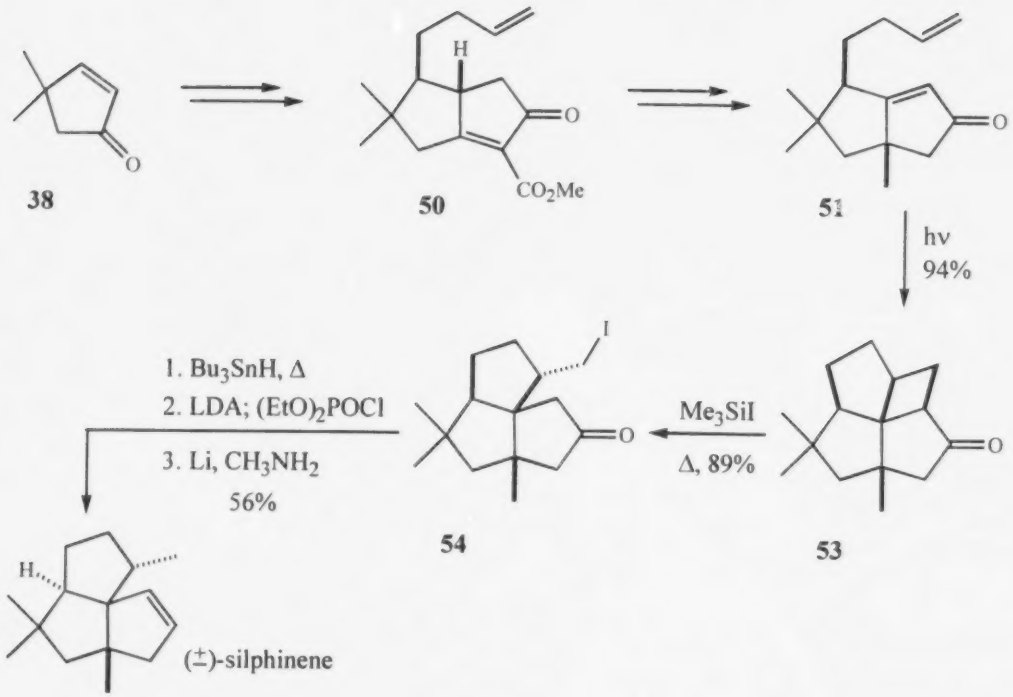
Ernst has shown[18] that acid chloride **45** can be converted to vinylketene **46**, which undergoes cycloaddition to form cyclobutanone **47** (Scheme 10). The necessary ring expansion[19] was accomplished by treating **47** with ethyl diazoacetate in the presence of $BF_3 \cdot OEt_2$, to give keto ester



Scheme 10

48. When this is heated under acidic conditions the angular triquinnane **49** is formed. Although **49** is not a natural product, it has the same relative stereochemistry at the ring junctions as isocomene.[20] Ernst has also used similar methodology to synthesize linear triquinnanes.[21]

Another use of [2+2] cycloaddition is seen in Crimmins's synthesis of (±)-silphinene (Scheme 11).[22] Key intermediate **51**, which was made in a series of steps (**38**→**50**→**51**), underwent photocycloaddition, affording cyclobutane **52**. At this stage all that remained in order to generate the triquinnane system was opening of the four-membered ring, and this was achieved by exposure to



Scheme 11

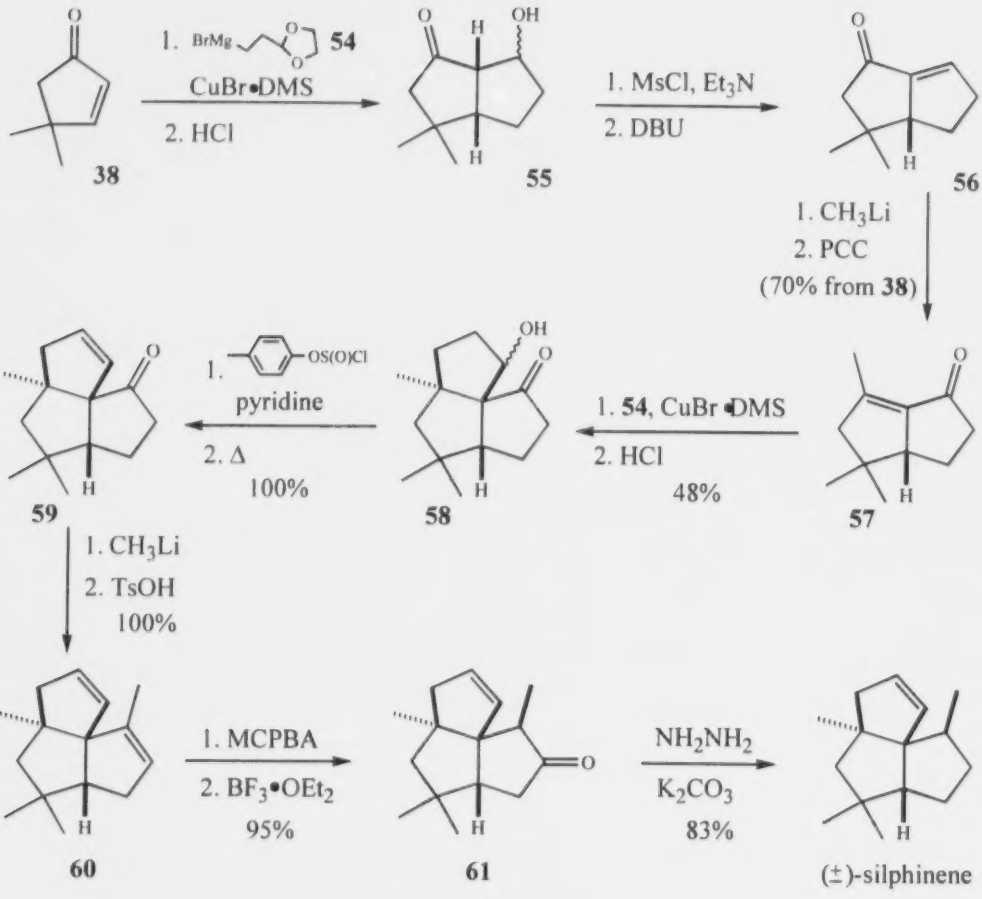
trimethylsilyl iodide (**53→54**). Reduction of the carbon-iodide bond, and then formation of an enolphosphate, followed by reduction, gave (±)-silphinene as the major product.

The steps leading to the formation of diquinnane **50** (Scheme 11) involved the use of an aldol reaction, and a detailed examination of this process in triquinnane synthesis will be given in the next section.

B. Triquinnane Syntheses Based on Classical Annulations

The intramolecular aldol reaction is a powerful tool for the formation of rings, and one might expect it to play a prominent role in triquinnane syntheses. Indeed, the literature contains many works in which key ring-forming processes make use of aldol chemistry in Robinson[23] annulations and related methods. Similarly, well-known transannular cyclizations[24] have also been applied in a number of syntheses.

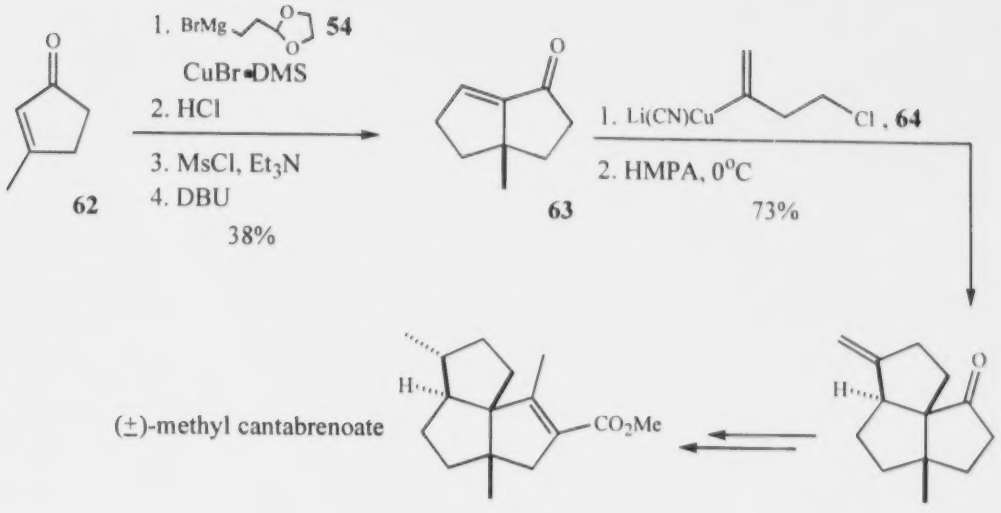
i. Use of Aldol Reactions for Robinson Annulation: A synthesis of (±)-silphinene (Scheme 12) by Paquette[25a] nicely illustrates the use of an aldol reaction. Cuprate addition of acetal **54** to enone **38**, followed by acid-promoted deprotection and aldol condensation gave alcohol **55**. Mesylation and elimination afforded enone **56**, and then methylation, followed by oxidative rearrangement, furnished enone **57**. A second iteration was now performed, using cuprate addition, deprotection, and aldol reaction, so as to arrive at alcohol **58**. The hydroxyl group was again eliminated (**58**→**59**), and methylation, followed by acid-promoted elimination, gave angular triquinnane **60**. To complete the synthesis, the more substituted double bond was epoxidized, and then Lewis acid-catalyzed epoxide opening and rearrangement led to ketone **61**. Finally, Wolff-Kishner reduction gave the natural product. Paquette has also used



Scheme 12

this tandem cuprate addition—aldol reaction procedure in syntheses of (±)-isocomene[25b] and (-)-silphiperfol-6-ene.[25c]

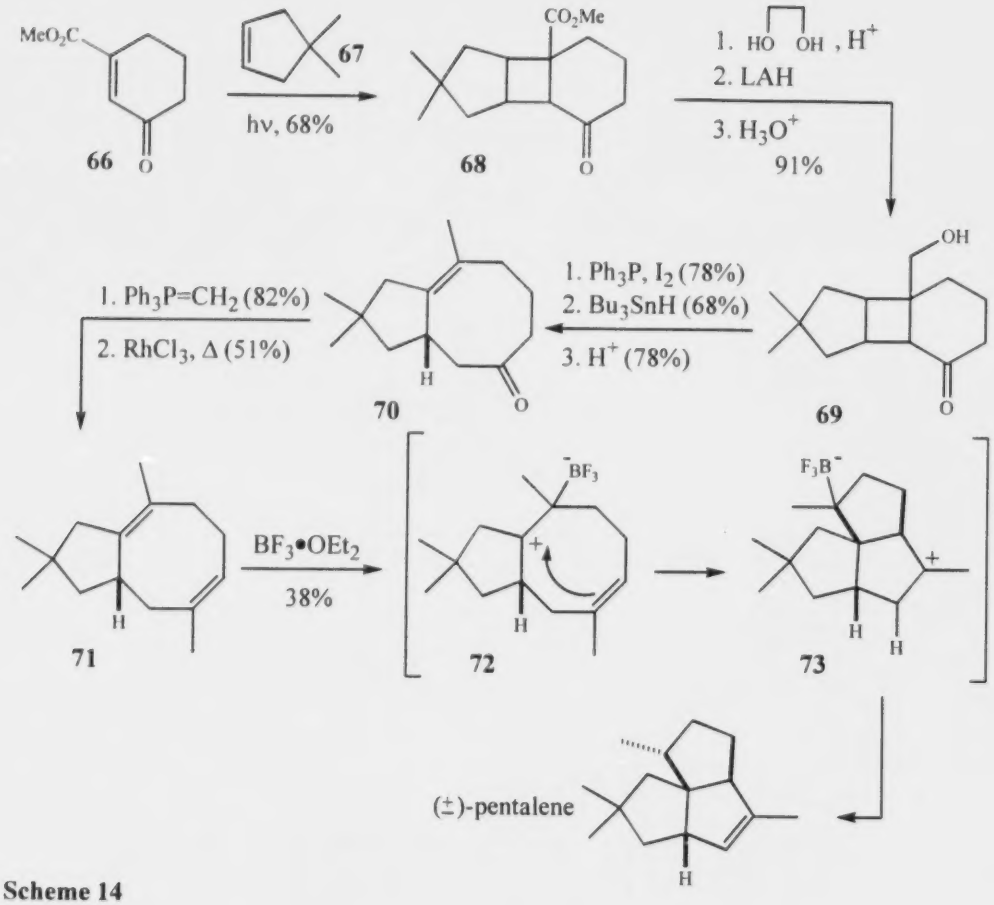
Piers has used similar methodology to construct ketone **65** (Scheme 13).[26] Enone **62** was converted into enone **63** using Paquette's protocol[25a] and then cuprate addition of chloride **64**, followed by chloride displacement, gave triquinnane **65**. This compound was taken through a number of



Scheme13

manipulations to afford (±)-methyl cantabrenonate, a derivative of the natural product cantabrenolic acid.

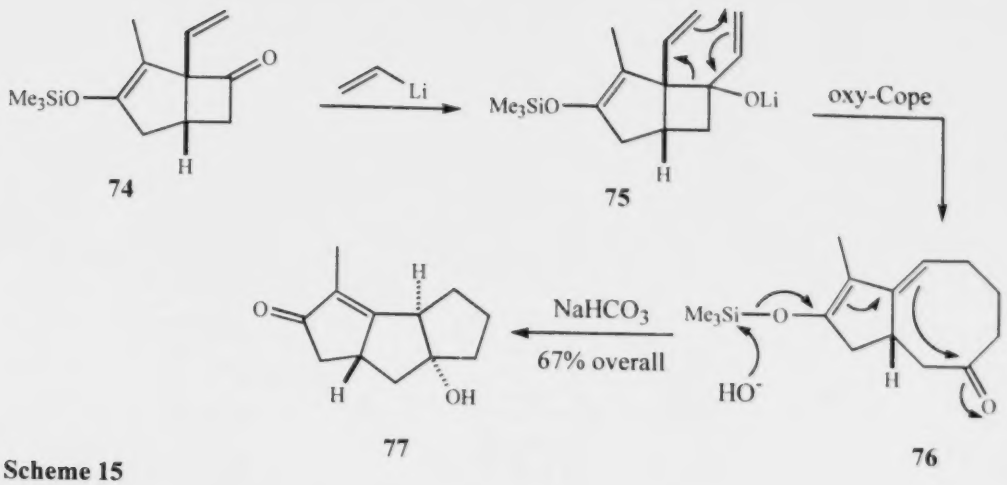
ii. Use of Transannular Cyclizations: Recently, Lange has reported[27] an efficient synthesis of ketone **70** from enone **66** (Scheme 14). [2+2] Cycloaddition with alkene **67** gave ester **68**, and this was reduced to alcohol **69**. Conversion to the corresponding iodide, followed by tin hydride reduction, afforded the desired ketone **70**, after silica-promoted isomerization of the double bond. Pattenden had previously converted **70** into (±)-pentalene[28,29] by first doing a Wittig reaction and then isomerizing the double bond so as to form diene **71**. Treatment with $BF_3 \cdot OEt_2$



Scheme 14

induced stereoselective transannulation (**72**→**73**), leading to the natural product.

Recently, Moore has developed a tandem oxy-Cope-transannular ring closure protocol,[30] for making linear triquinnanes (Scheme 15). Cyclobutanones such as **74** can be treated with vinyllithium and the resulting alkoxide (**75**), when warmed, undergoes oxy-Cope rearrangement affording ketone **76**. Desilylation then initiates transannular cyclization to



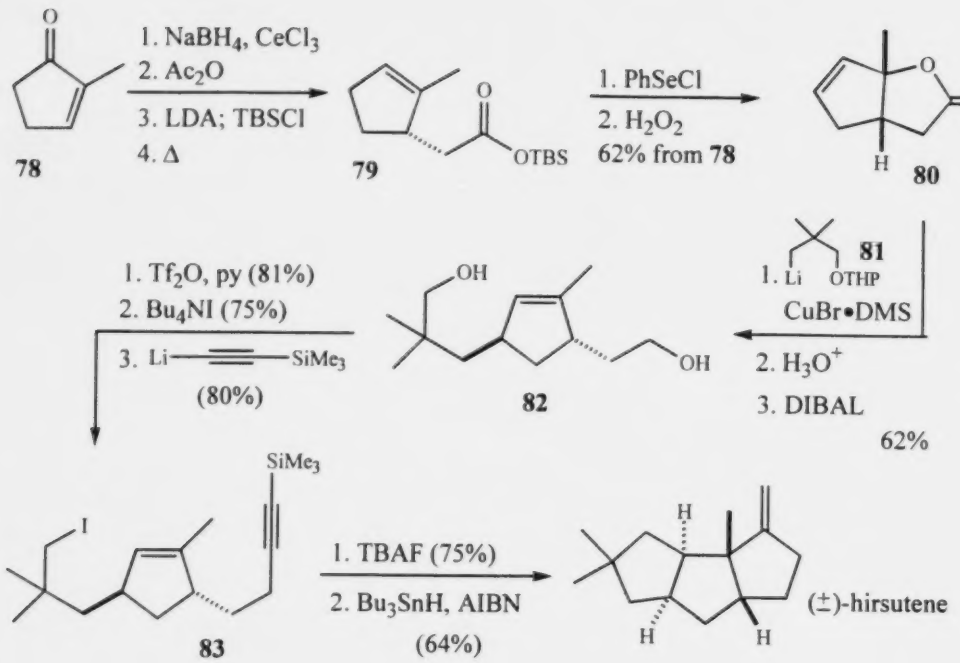
Scheme 15

the triquinnane **77**. Although this procedure has not been used in a natural product synthesis, the high degree of functionality in **77** makes its elaboration into a natural triquinnane a realistic possibility.

C. Triquinnane Syntheses Based on Radical Cyclization

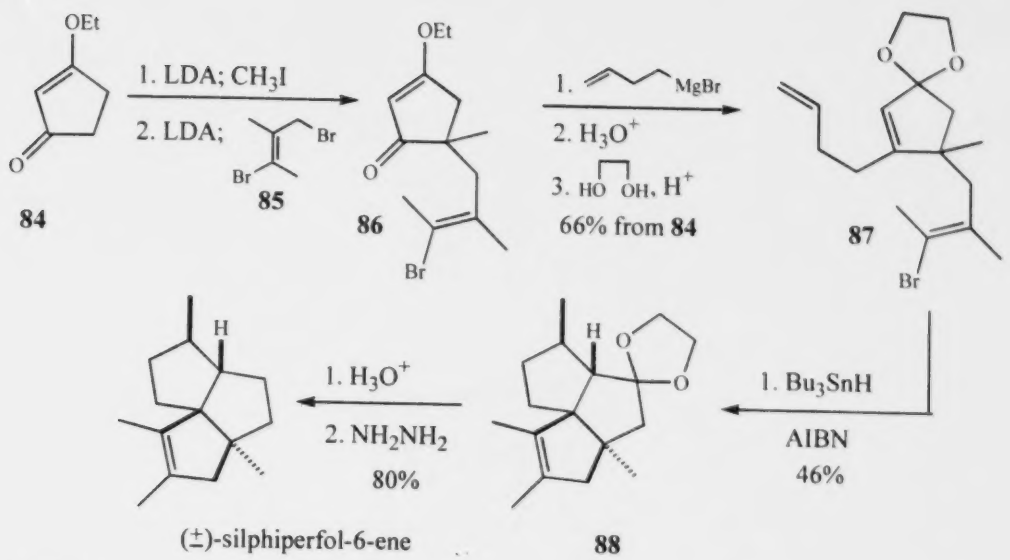
In contrast to the classical annulation methods described in the previous section, radical cyclization has emerged only recently as a powerful technique for the construction of five-member rings, but a number of triquinnane syntheses already make use of radical cyclization in key ring-forming steps.

Curran's synthesis of (±)-hirsutene,[31] which used radical cyclization to form two of the rings,[32] began with enone **78** (Scheme 16). Reduction, acetylation, and Ireland ester enolate rearrangement gave silyl ester **79**, and this



Scheme 16

underwent lactonization in the presence of phenylselenenyl chloride. Oxidation and elimination of the resulting selenide afforded lactone **80**, as expected. The lactone was opened with organometallic reagent **81**, the THP protecting group was removed, and the resulting hydroxy acid was reduced to diol **82**. This was converted to the diiodide, and then the more accessible primary iodide was preferentially displaced by lithium trimethylsilylacetylide to produce radical precursor **83**. The silyl group was removed, and treatment with tin hydride resulted in regio- and stereoselective closure of two rings, giving (±)-hirsutene directly.

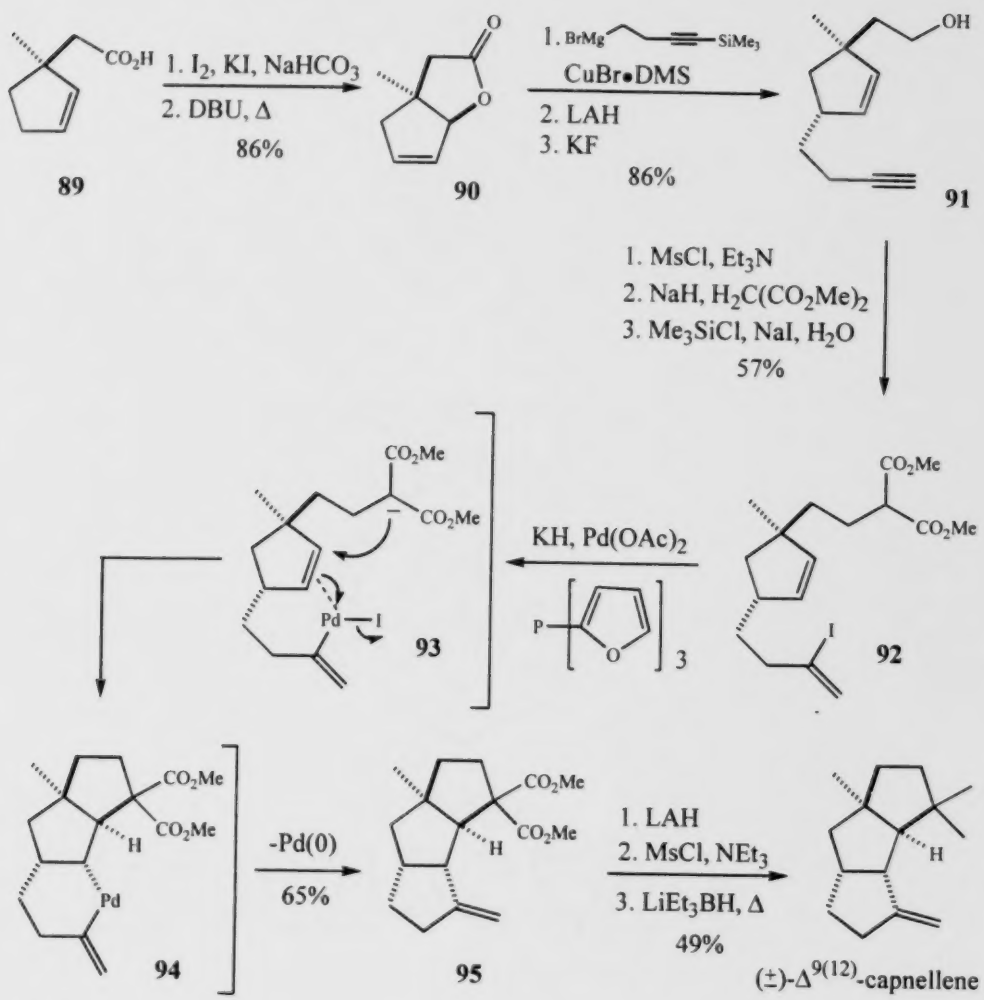


Scheme 17

Another example of this tandem radical cyclization is seen in Curran's synthesis of (±)-silphiperfol-6-ene (Scheme 17).[33] Sequential alkylation of enone **84** with methyl iodide and dibromide **85**, produced the doubly alkylated product **86**. Radical precursor **87** was then formed after Grignard addition, hydrolysis, and ketone protection. Tandem radical cyclization proceeded smoothly to give angular triquinnane **88**. Removal of the protecting group and Wolff-Kishner reduction then led to the natural product.

D. Triquinnane Synthesis Based on Palladium Coupling

Another reaction that has recently emerged as a technique for forming rings is palladium catalyzed cyclization. Palladium has been used in metallo-ene



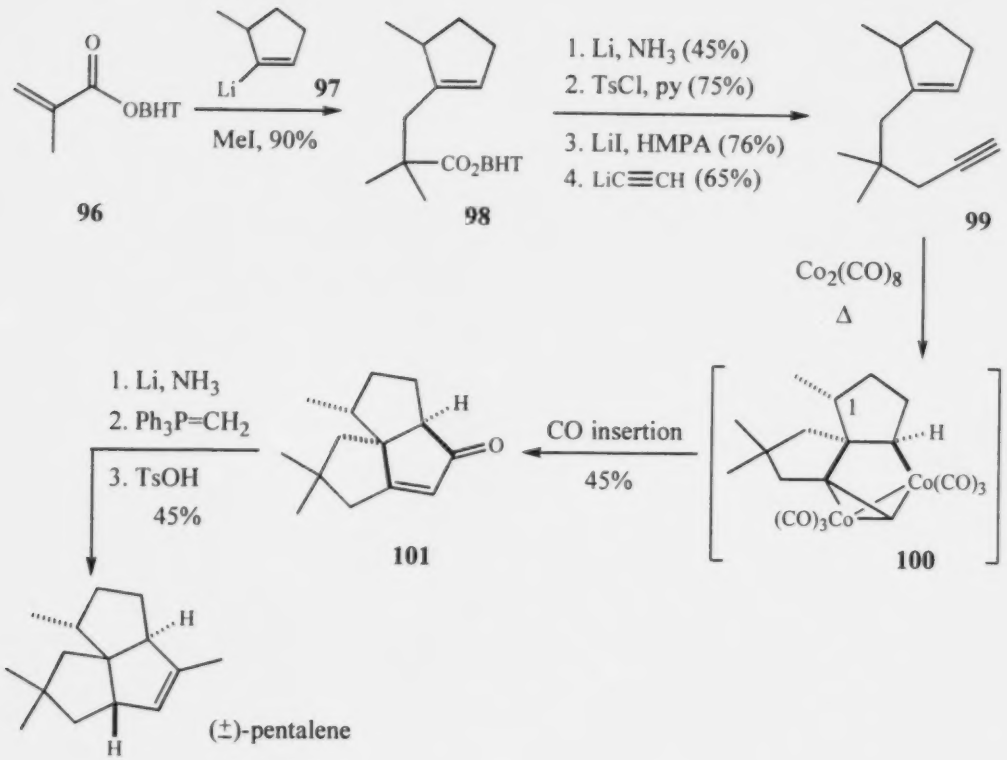
Scheme 18

cyclizations[34] during hirsutene syntheses,[35,36] and in a type of Wacker process, during a synthesis of (±)-$\Delta^{9(12)}$capnellene.[37] In the latter case (Scheme 18), iodolactonization and elimination converted acid **89** into lactone **90**. Cuprate addition, hydride reduction, and desilylation afforded alcohol **91**. The hydroxyl group was

mesylated and displaced with dimethyl sodium malonate, and the alkyne was then converted to an alkenyl iodide, so bringing the synthesis as far as **92**. The key tandem-palladium cyclization was then performed. In this process the enolate nucleophile attacks the activated σ-vinyl palladium species (**93→94**) and reductive elimination produces triquinnane **95**. The synthesis was then completed by reduction of the *gem*-diester to a *gem*-dimethyl group.

E. Triquinnane Synthesis Based on the Pauson-Khand Reaction

Another metal-mediated cyclization is the Pauson-Khand reaction.[38] This has often been used as a convenient route to diquinnanes,[39] and recently has been applied to triquinnanes.[40,41] Schore has reported a synthesis of (±)-pentalene[42] that is based on a stereoselective intramolecular Pauson-Khand reaction (Scheme 19). Conjugate addition of **97** to α,β-unsaturated ester **96**, followed by enolate trapping with methyl iodide, gave ester **98**. The ester function was reduced, and the resulting hydroxyl group was converted to a leaving group, which was displaced to produce key enyne **99**. Treatment with $Co_2(CO)_6$ induced stereoselective cycloaddition (**99→100**), in which the bulky alkyne-cobalt complex was orientated away from the methyl



Scheme 19

group on C(1), giving, after CO-insertion, enone **101**. Reduction of the double bond, Wittig reaction, and double bond isomerization then produced the desired natural product.

F. Conclusion

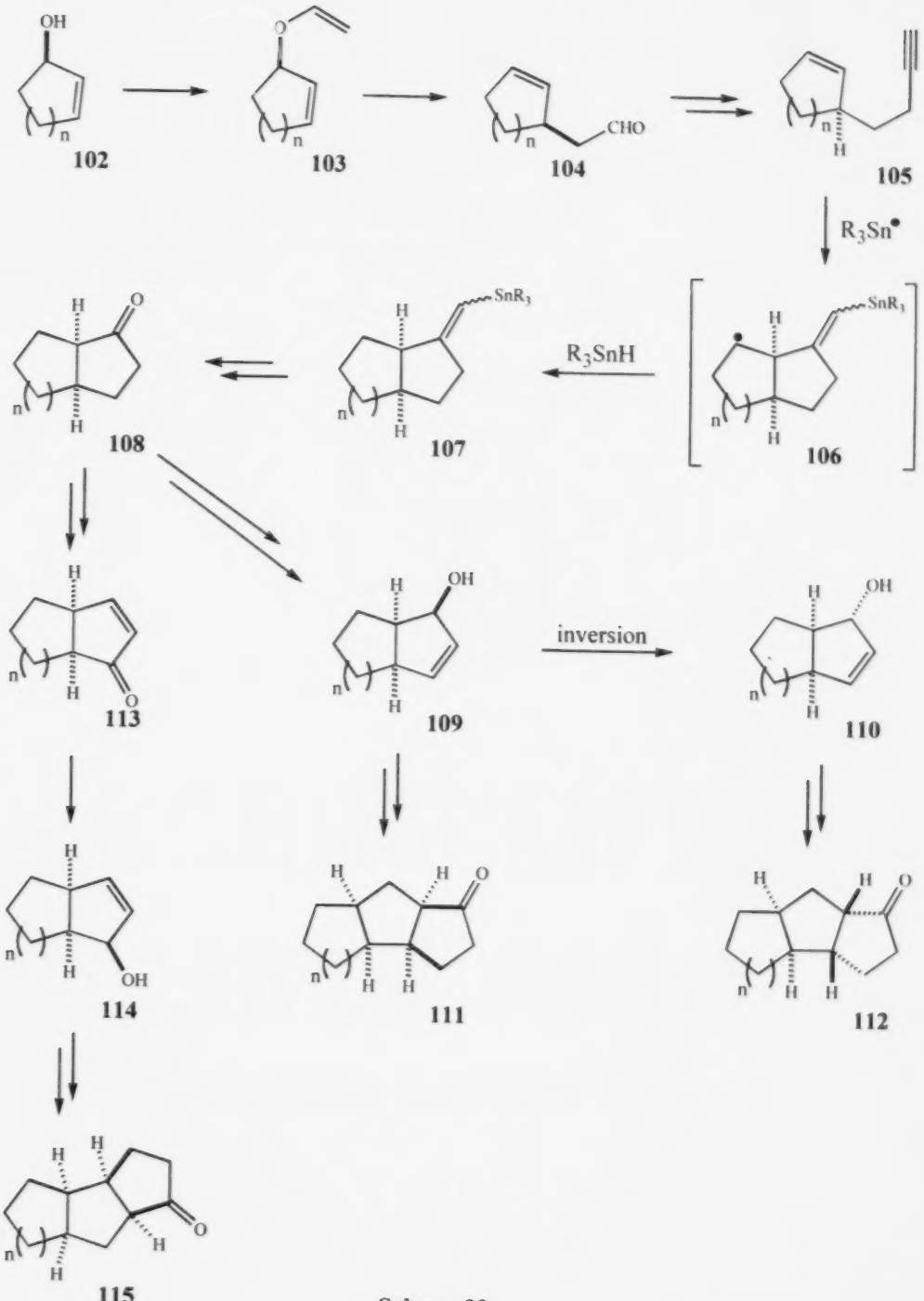
The impressive examples covered in this review have focused mainly on cases where two or more rings of the triquinnane are formed using the key reaction in question. There are also many innovative methods in which rings are constructed by a combination of these or other reactions,

such as Nazarov cyclization,[43] spiroannulation,[44] [3+2] annulation,[45] and the ene reaction.[46] Triquinnanes are important synthetic targets because they serve as a test bed for new methodology, and because some members of the class have significant biochemical properties.[5] It is likely that they will continue to receive close attention from synthetic chemists.

Results and Discussion:

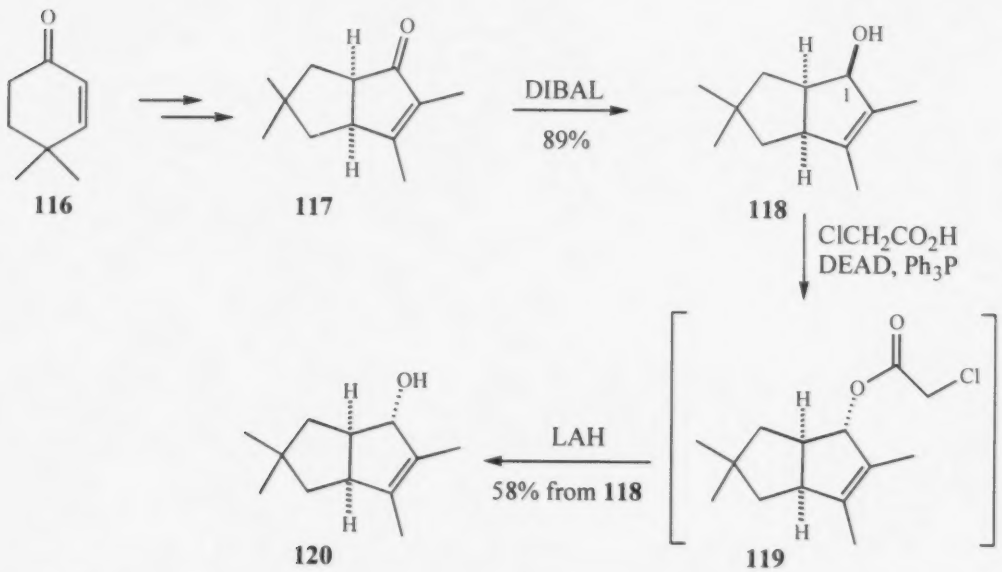
Prior to our synthesis of racemic ceratopicanol,[47] Mehta had published a synthesis of the unnatural antipode.[48] His approach made use of Eaton's Reagent[49] in an intramolecular acylation that gave a key cyclopentenone intermediate. Quite recently, a third, and very efficient, synthesis of ceratopicanol has been reported.[50] This synthesis made use of the arene-olefin photocycloaddition[7] that was discussed in section A.i of the introduction.

Our own synthesis of ceratopicanol[47] was undertaken as a test of iterative cyclopentannulation methodology that had been developed in our group by Hartford Manning.[47a,51] The principle of the method is summarized in Scheme 20. An allylic alcohol can be converted by Claisen rearrangement (**102→103→104**) and homologation (**104→105**) into an enyne in which the acetylenic chain is on the same face as the original hydroxyl. Treatment with stannyl radicals then gives a vinyl stannane (**105→106→107**) which is convertible into a ketone (**107→108**). Since ketones may be easily desaturated and reduced, compounds of type **108** are synthetically equivalent to allylic alcohols **109**. Stereochemical inversion would serve to convert **109** into its epimer **110**. Both **109** and **110** are, of course, members of the allylic alcohol class that was used to begin the sequence.


OH
n
102
O
n
103
CHO
n
104
n
H
105
R3Sn•
SnR3
H
n
H
106
R3SnH
SnR3
H
n
H
107
H
O
n
H
108
H
n
H
O
113
H
OH
n
H
109
inversion
H
OH
n
H
110
H
n
OH
114
H
H
O
n
H
H
111
H
H
O
n
H
H
112
H
H
n
H
O
H
115

Scheme 20

In principle, therefore, repetition of the whole process would result in annulation of an additional ring on the same face as the new hydroxyl (**109→111**) and (**110→112**). There is also the possibility of 1,3-oxygen transposition,[52] and if this is incorporated into the sequence, the next ring would be fused on a different edge of the substrate (**108→113→114→115**).

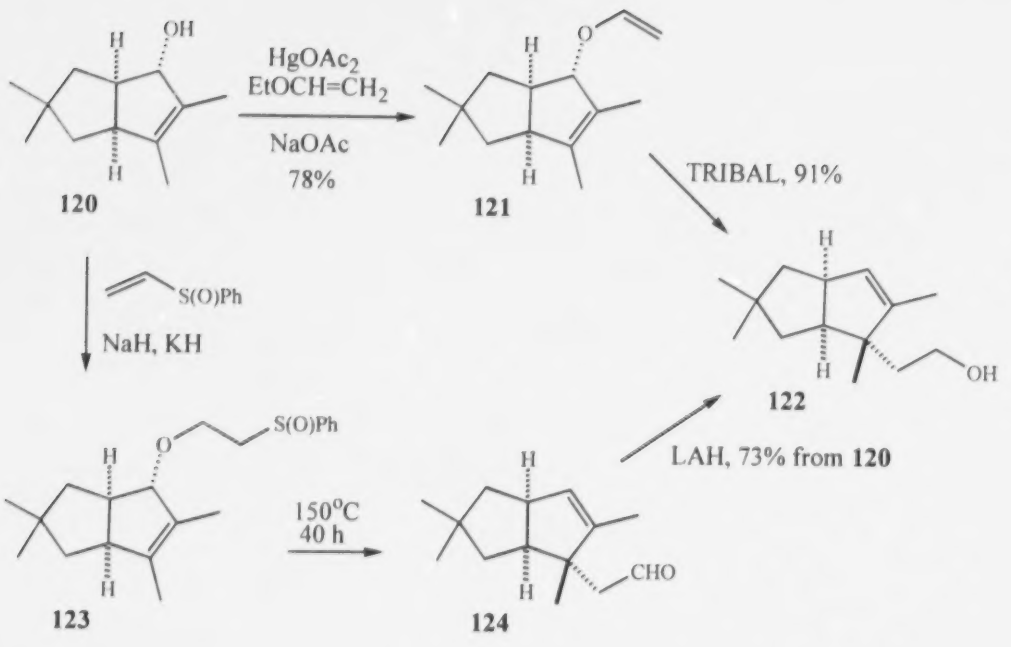


Scheme 21

Our synthesis of racemic ceratopicanol began (Scheme 21) with the known[53] enone **117**, easily made from commercially available enone **116**. It was our intention to annulate the third ring onto diquinnane **117** using the sequence outlined in Scheme 20. Our starting material (**117**)

was reduced to allylic alcohol **118** using DIBAL. Careful work-up (see experimental section) was required to avoid elimination of the intermediate oxo-aluminum moiety. Next, inversion of stereochemistry at C(1) was required so as to obtain, eventually, the desired stereochemistry at the methyl-substituted bridgeheads of the natural product. The inversion was carried out by first converting allylic alcohol **118** into ester **119**, using chloroacetic acid in the presence of triphenylphosphine, diethyl azodicarboxylate, and benzene.[54] Ester **119** was then reduced with LAH, to allylic alcohol **120**. Examination of the literature revealed that Mitsunobu inversions of sterically hindered allylic alcohols are somewhat troublesome[55] and, indeed, for our compound, of several procedures that were attempted,[56] only the conditions noted above gave an acceptable result.

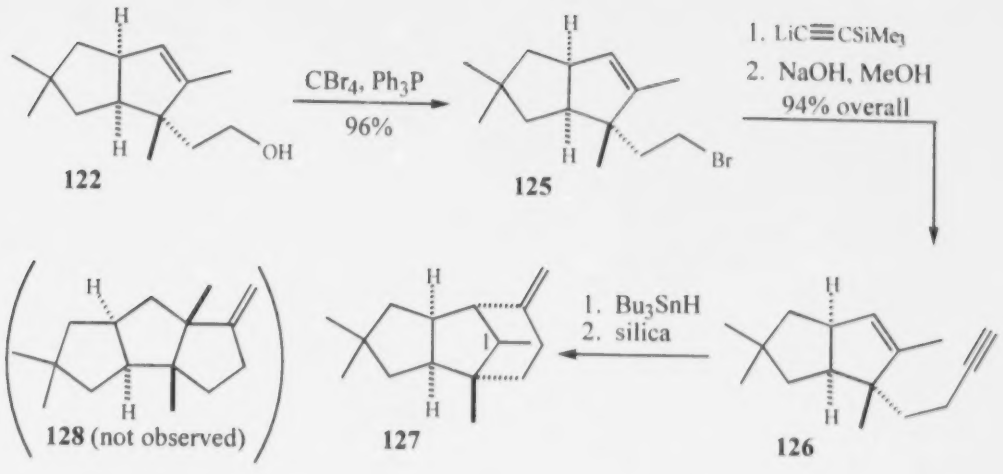
We next wanted to convert allylic alcohol **120** into alcohol **122**, and found that this could be accomplished by either of two routes (Scheme 22). Initially **120** was converted into vinyl enol ether **121**, using ethyl vinyl ether and mercuric acetate in a reaction medium buffered by sodium acetate.[57] Compound **121** was then treated with triisobutylaluminum,[58] a reagent which first catalyzed Claisen rearrangement and then effected Meerwein-Ponndorf-Verley reduction to give alcohol **122** directly. The yield obtained in the conversion of **120**→**121** was not consistently



Scheme 22

reproducible and so an alternative procedure[59] was investigated. Allylic alcohol **120** was converted into sulfoxide **123**, using phenyl vinyl sulfoxide. Thermal Claisen rearrangement then afforded aldehyde **124**, and this was reduced (LAH) to alcohol **122**. Both routes gave about the same overall yield (71-73%), but the second route was more reliable.

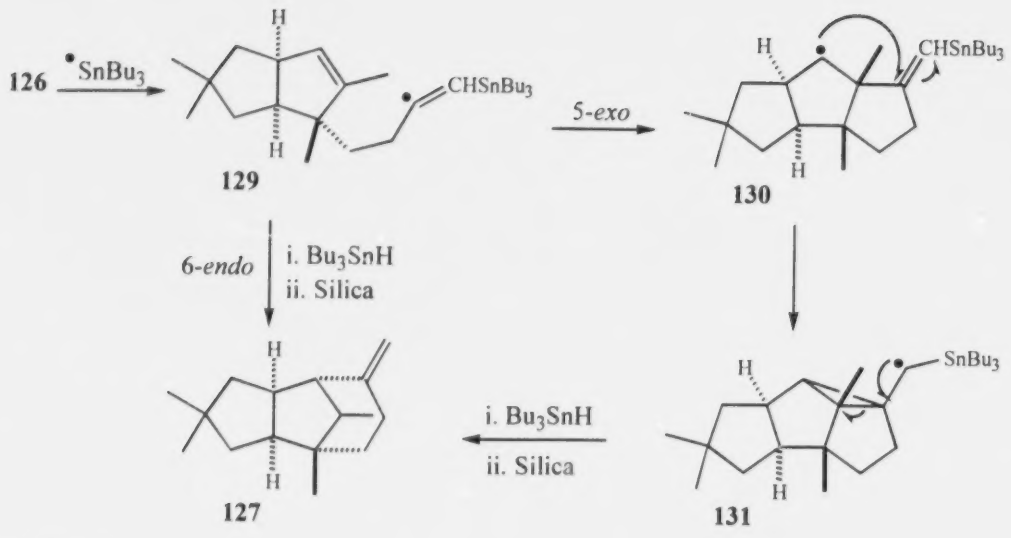
Alcohol **122** was converted efficiently (Scheme 23) into the corresponding bromide (**125**) using triphenylphosphine and carbon tetrabromide. The halogen was then displaced with lithium (trimethylsilyl)acetylide.[60] Methanolic sodium



Scheme 23

hydroxide work-up effected desilylation[61] to afford enyne **126**, which was our desired radical precursor. When the enyne was treated with tributyltin hydride (0.01-0.07 M) in refluxing benzene, with AIBN as an initiator, only alkene **127** was isolated after exposure to silica gel (for protodestannylation). Compound **127** was a single isomer, but the relative stereochemistry at C(1) could not be established by NOE experiments. None of the desired alkene **128** was observed in the radical cyclization.

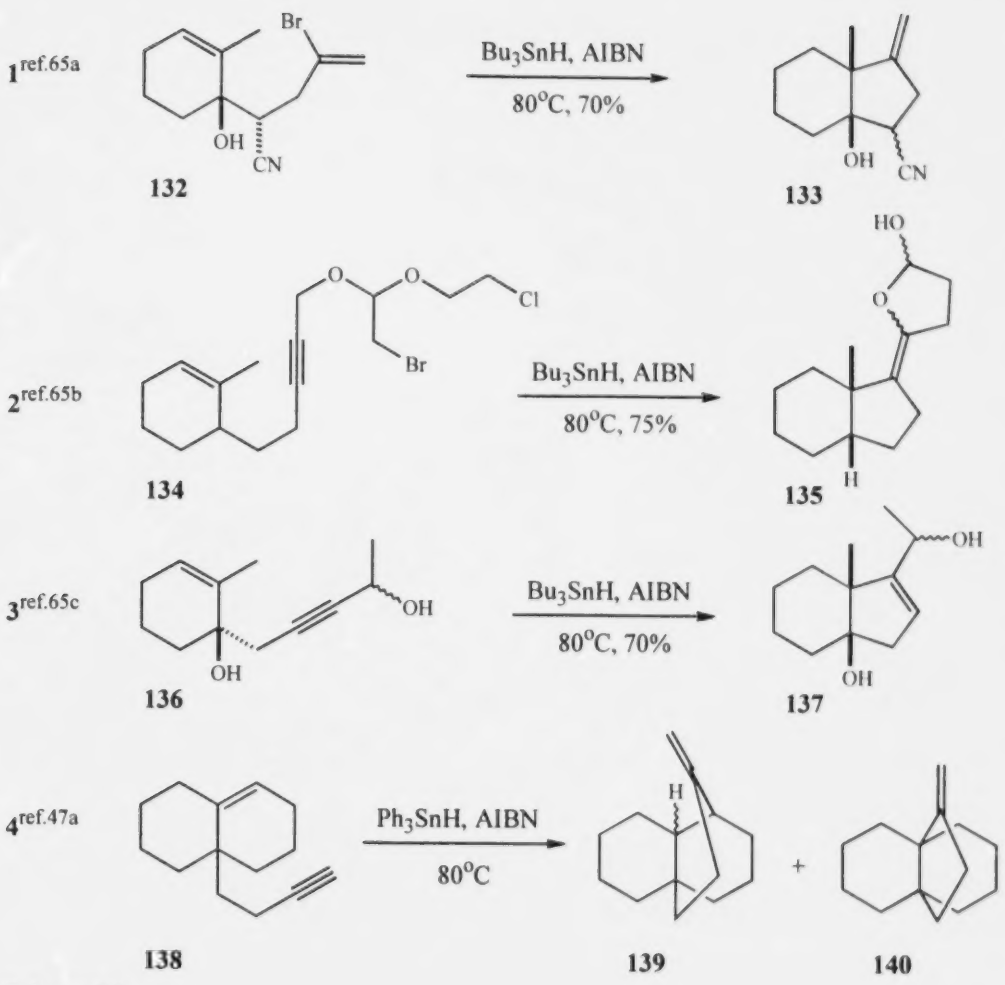
Formation of **127** could occur (Scheme 24) either by direct 6-*endo* closure (**129→127**), or by the normal 5-*exo* pathway (**129→130**), followed by rearrangement[62] (**130→131→127**). If the rate of bimolecular hydrogen abstraction from stannane by the hindered radical **130** is



Scheme 24

slow, rearrangement of **130** to **127** need not be unusually fast; however, we were unable to rule out the possibility that formation of **127** is an example of kinetically preferred direct 6-*endo* closure.[63] For example, in an attempt to trap radical **130**, use of a higher stannane concentration (1.1 M) still gave **127** (and not the desired **128**), as well as hydrostannylation products of the triple bond. Furthermore, when we attempted the radical cyclization in the presence[64] of a trace of PhSeSePh - in the hope of trapping **130** - the outcome was unchanged.

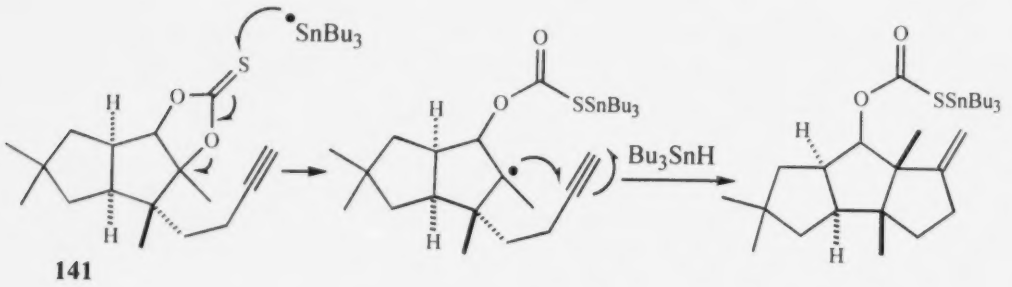
It is not clear why anomalous behavior is observed in this case, since several examples are known (Scheme 25, entries 1-3) in which vinyl radicals cyclize onto proximally substituted non-conjugated double bonds.[65] However, in



Scheme 25

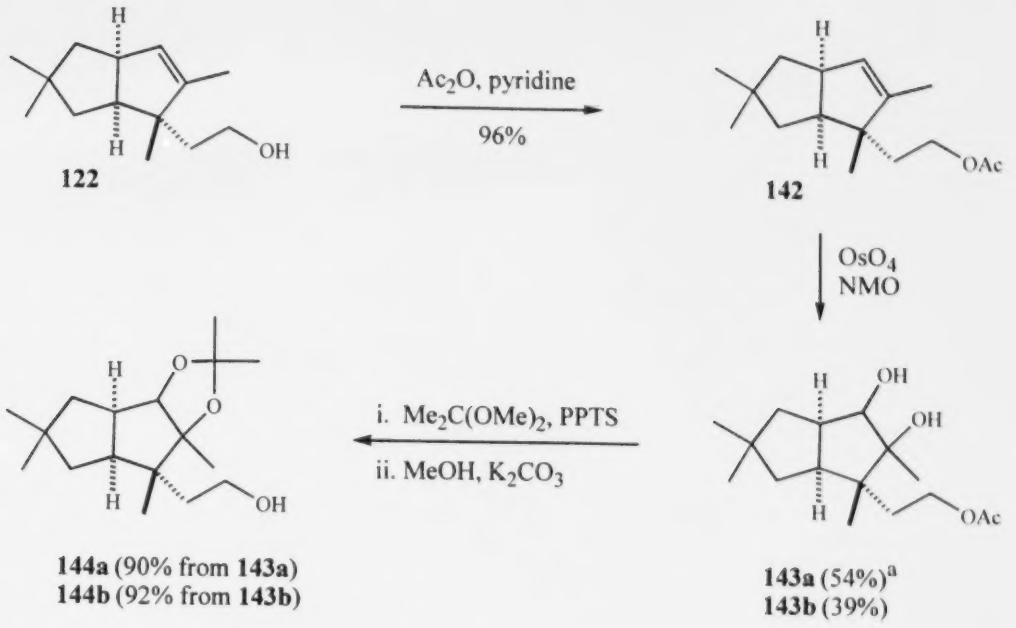
related work, by Darrin Mayhew[47a] of this laboratory, radical cyclization of **138** (entry 4) proceeded to give a mixture of three inseparable products, and, on the basis of ^{13}C-NMR measurements, the structures are believed to correspond to the product of formal 6-*endo* closure (**139**), and the expected material (**140**) from the 5-*exo* pathway.

In any event, we were forced to modify the approach, and we now tried to generate the radical at a different position so that closure would occur *onto* the triple bond, as depicted in Scheme 26.



Scheme 26

In order to construct the substrate required by Scheme 26, alcohol **122** was first converted into acetate **142** (Scheme 27). This compound was then treated with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide,[66] to afford a separable mixture of diols (**143a** with hydroxyl groups *anti* to *O*-acetyl chain and **143b** with hydroxyl groups *syn* to *O*-acetyl chain). Our stereochemical assignments to the diols were made on the basis of proton NMR coupling constants in the derived hydroxy ketals **144a** and **144b** (see experimental section). The vicinal diols **143a** and **143b** were protected as their acetonides, not only to settle the stereochemical assignment, but also as part of the synthesis, and the



144a (90% from **143a**)
144b (92% from **143b**)

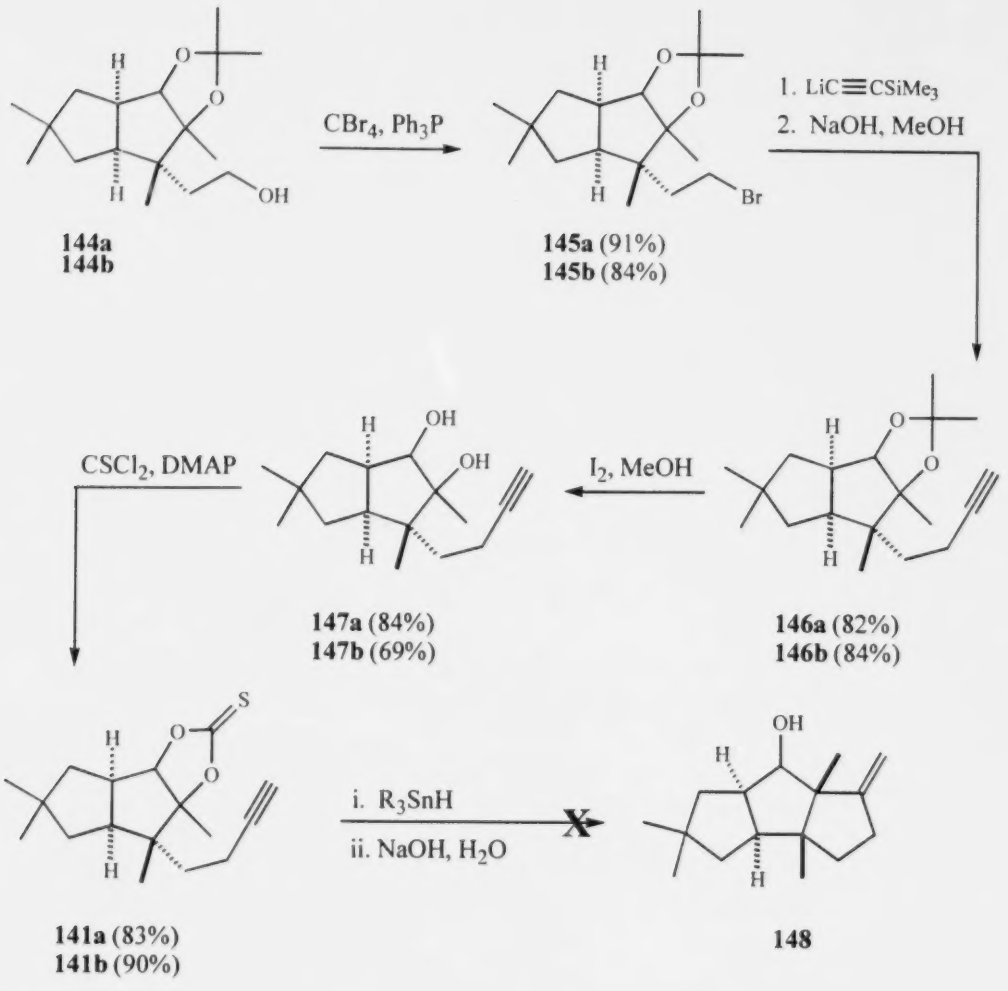
143a (54%)[a]
143b (39%)

[a] Compound **143a** has hydroxyl groups *anti* to *O*-acetyl chain
Compound **143b** has hydroxyl groups *syn* to *O*-acetyl chain

Scheme 27

acetate protecting groups were then removed (K_2CO_3, MeOH) to liberate the primary alcohols **144a** and **144b**, respectively.

These alcohols were manipulated (Scheme 28), through bromination (**144a→145a** and **144b→145b**) and chain extension (**145a→146a** and **145b→146b**), in the manner described earlier. Iodine was used to remove the acetonide protecting groups,[67] affording vicinal diols **147a** and **147b**. These were acylated with thiosphosgene, in the presence of DMAP, to produce the thionocarbonates **141a** and **141b** that were required for implementation of Scheme 26.



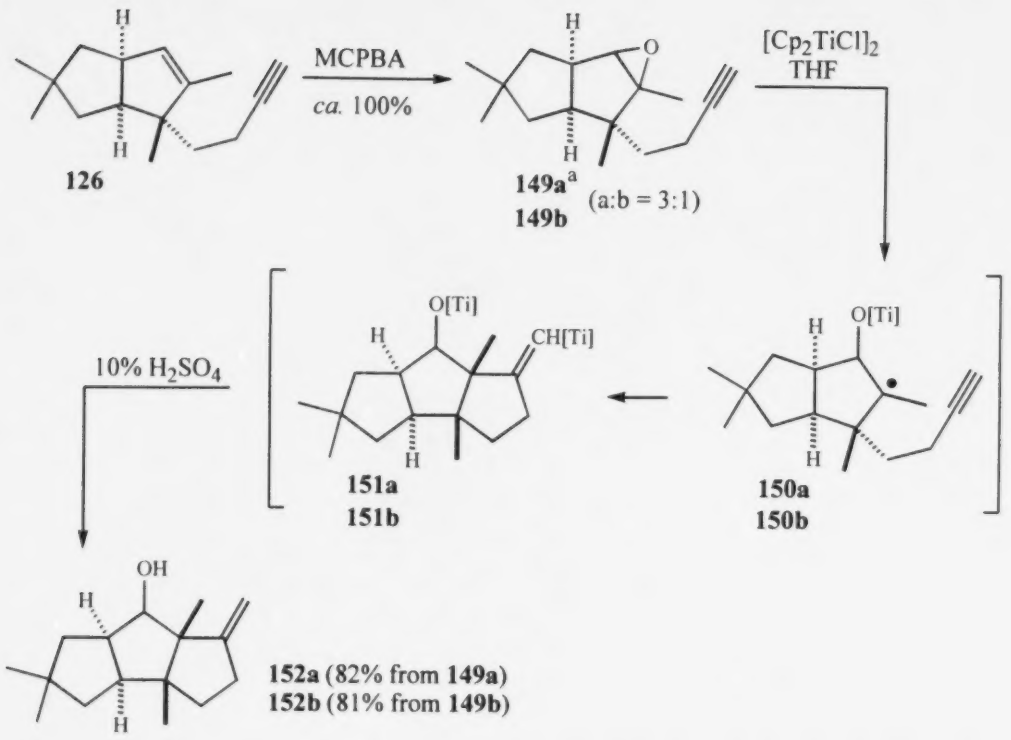
Scheme 28

Unfortunately, reduction of **141a** or **141b** with triphenyltin hydride or tributyltin hydride gave quite complex mixtures under what we judged to be appropriate and standard conditions for radical cyclization, and the products of the desired type (**148**) did not appear to be present—at least as judged by 200 MHz ^{1}H NMR spectra of the reaction mixtures. It would have been not only helpful to

us, but also interesting, to have obtained readily isolable products, because some work has been reported[68] on stannane reduction of unsymmetrical thionocarbonates, and formation of either the less substituted or the more substituted radical—as we had wanted (*cf.* Scheme 26)—has been observed. However, exactly what controls the regiochemistry is not fully understood, and the status (primary, secondary, or tertiary) of the potential carbon radical product is evidently not the only important factor.

Fortunately, radical cyclization was soon easily accomplished after we recognized[69] that an epoxide can be made to behave (Scheme 29) in a manner appropriate for the task at hand.

Epoxidation of enyne **126** with MCPBA gave two separable epoxides **149a** (oxygen *anti* to the acetylenic chain) and **149b** (oxygen *syn* to the acetylenic chain). Stereochemical assignments to the epoxides were made by NOE measurements on ketone **155b** (Scheme 30) derived from epoxide **149b** (see experimental section). Compounds **149a** and **149b** were each treated with bis(cyclopentadienyl)titanium(III) chloride,[70,71] which opened the epoxide regioselectively, to give the more stable tertiary radicals **150a** and **150b**, respectively. Radical cyclization then proceeded in a 5-*exo* fashion to intermediates **151a** and **151b** which, upon treatment



126

149a[a] (a:b = 3:1)
149b

151a
151b

150a
150b

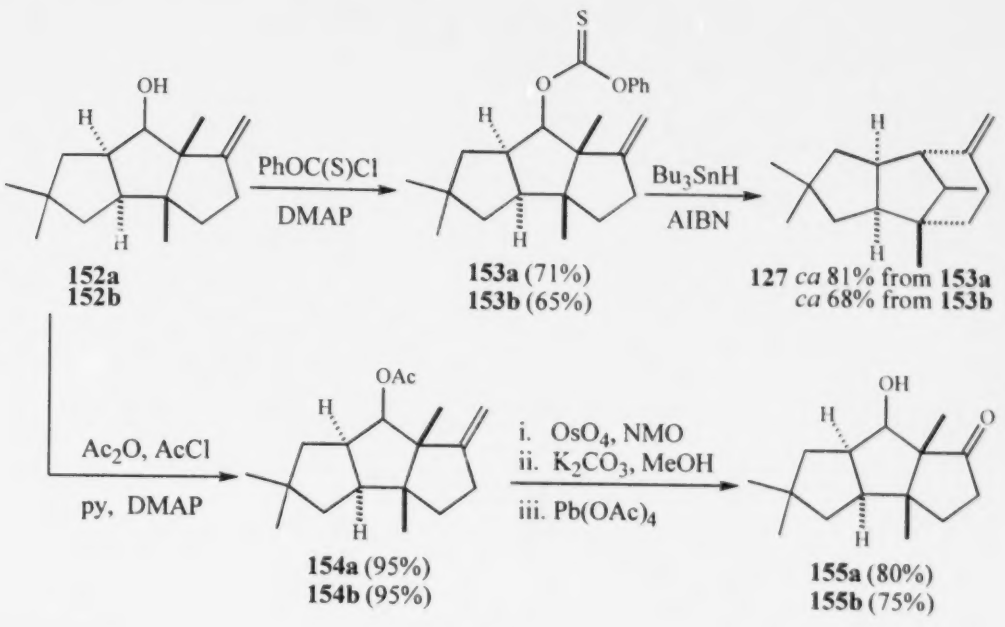
152a (82% from **149a**)
152b (81% from **149b**)

[a] Compound **149a** has oxygen *anti* to the acetylenic chain
Compound **149b** has oxygen *syn* to the acetylenic chain

Scheme 29

with aqueous acid, gave the corresponding alkenes **152a** and **152b**.

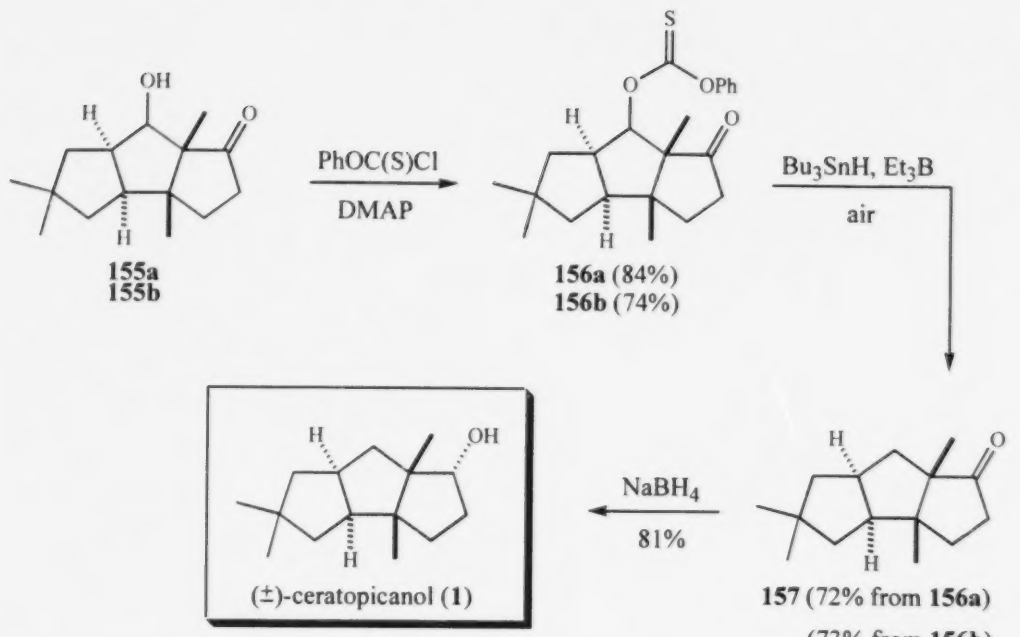
With the required carbon framework now constructed, a little experimentation was required to find the best way of performing the last few steps. Radical deoxygenation of **152a** and **152b** by means of the corresponding phenoxythiocarbonyl esters (**153a** and **153b**)[72] was attempted first, so as to converge the two routes (Scheme 30). Interestingly though, treatment of either **153a** or **153b** with



Scheme 30

tributyltin hydride resulted in formation of alkene **127**, the product obtained in our initial radical cyclizations (Scheme 23). In order to avoid the rearrangement, **152a** and **152b** were individually acetylated, giving **154a** and **154b**, dihydroxylated with osmium tetroxide, and hydrolyzed (K_2CO_3, MeOH). The resulting triols (not shown in Scheme 30) responded in the normal way to the action of lead tetraacetate, affording hydroxy ketones **155a** and **155b**.

Deoxygenation of these compounds was accomplished (Scheme 31) by first converting them into the corresponding phenoxythiocarbonyl esters (**156a** and **156b**).[72] These were then treated with tributyltin hydride in the presence of triethylborane and air[73] to give ketone **157**. When

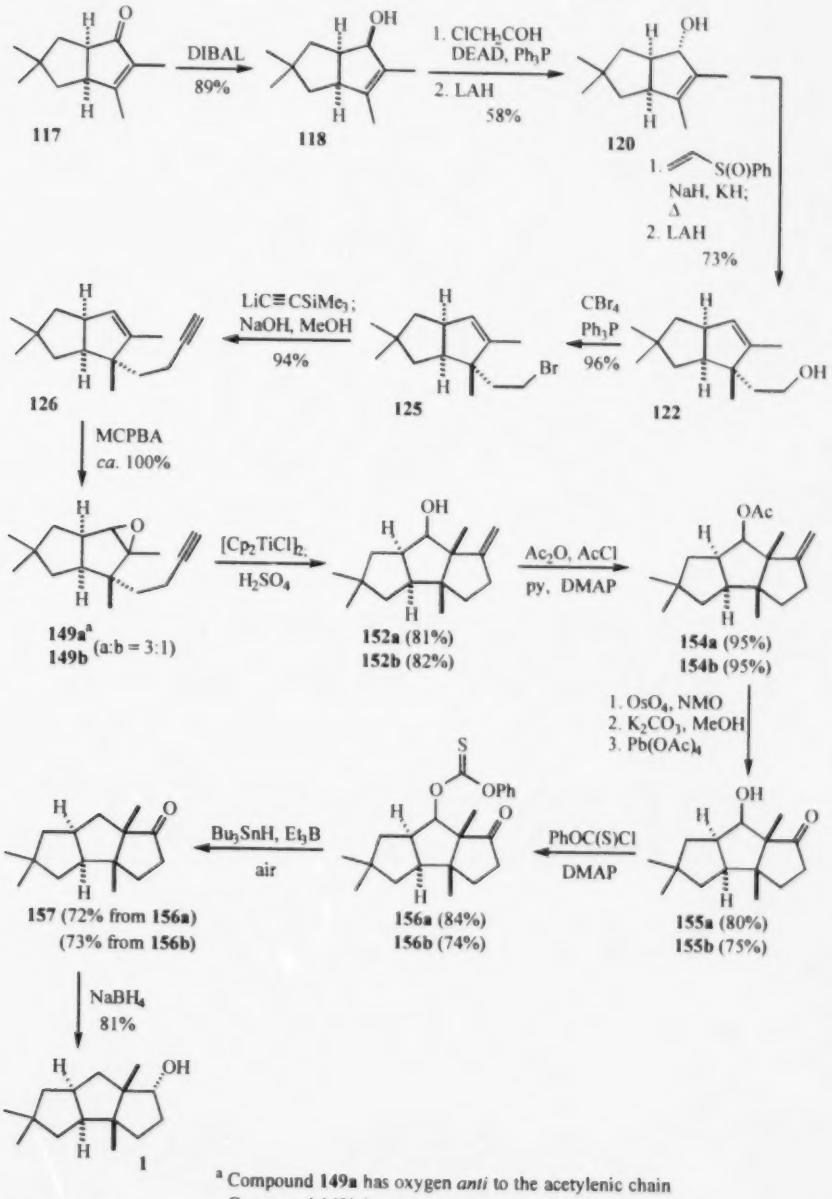


Scheme 31

deoxygenation was attempted using thermal initiation by AIBN in refluxing toluene, appreciable ring expansion occurred,[74] analogous to that observed in the conversion of **153a** or **153b** into **127** (Scheme 30). Fortunately, the milder borane-mediated procedure was satisfactory. Finally, reduction with sodium borohydride gave crystalline (±)-ceratopicanol to complete our synthesis.

The discussion of our route, given above, includes a number of digressions, and Scheme 32 summarizes the final version of the synthesis. Although the route is quite long (21 steps including synthesis of **117**) it provides, by use of the tandem Claisen rearrangement — radical cyclization

procedure, stereospecificity during formation of the ring junctions which is, of course, a desirable, yet not easily accomplished, feature of any natural product synthesis.



[a] Compound **149a** has oxygen *anti* to the acetylenic chain
Compound **149b** has oxygen *syn* to the acetylenic chain

Scheme 32

Experimental:

General Procedures: Argon was purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled before use. Petroleum ether refers to the fraction bp 35-60 °C.

Products were isolated from solution by evaporation under water pump vacuum at, or below, 30 °C, using a rotary evaporator.

Temperatures recorded for Kugelrohr distillations refer to air-bath temperatures and are not true boiling points. The values indicate the temperature at which the distillate begins to condense in the receiving bulb.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light or by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry THF was distilled from Na and benzophenone ketyl. Dry PhH was distilled from Na. Dry *i*-Pr_2NH, CH_2Cl_2, MeOH, pyridine, DMF, and HMPA were distilled from CaH_2, the last two solvents being distilled under water pump vacuum. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

Infrared spectra were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent and using potassium bromide plates.

Proton nuclear magnetic resonance spectra were recorded with Bruker WP-200 (at 200 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded with Bruker WP-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker AM-400 (at 100.6 MHz) spectrometers using $CDCl_3$ as an internal standard. The symbols s', d', t', and q' used for ^{13}C NMR spectra indicate 0, 1, 2,or 3 attached protons.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70eV.

Microanalyses were performed by the microanalytical laboratory of this Department.

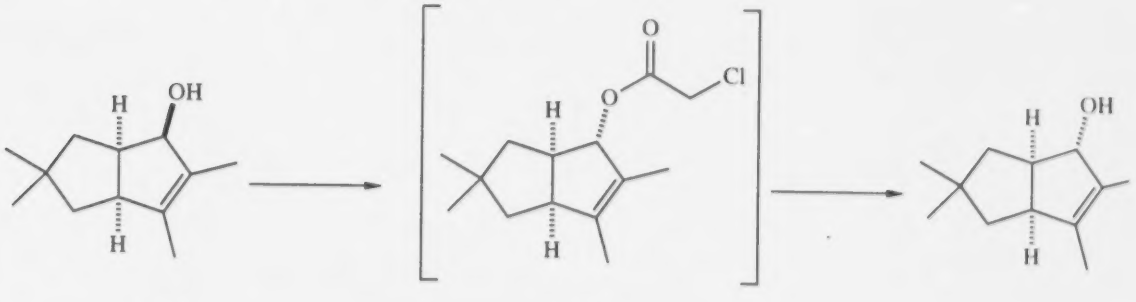
(1α,3aβ,6aβ)-(±)-1,3a,4,5,6,6a-Hexahydro-2,3,5,5-tetramethyl-1-pentalenol (118).

117 **118**

DIBAL (1 M in CH_2Cl_2, 4.3 mL, 4.3 mmol) was added dropwise over *ca.* 20 min to a cooled (0 °C) and stirred solution of enone **117**[53] (385.1 mg, 2.16 mmol) in CH_2Cl_2 (20 mL). After 2 h the solution was added dropwise over *ca.* 30 min to a cooled (-78 °C) and stirred slurry of flash chromatography silica gel (*ca.* 10 g) in CH_2Cl_2 (100 mL). The cooling bath was removed and, when the temperature of the mixture reached 0 °C, water (8 mL) was added. The mixture was filtered through a pad (2 x 6 cm) of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 18 cm), using 10% EtOAc-hexane, gave allylic alcohol **118** (349.3 mg, 89%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3348 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.04 (s, 3 H), 1.11 (dd, *J* = 7.5, 5.0 Hz, 1 H), 1.26 (d, *J* = 8.0 Hz, 1 H), 1.32-1.48 (m, 2 H), 1.56 (dd, *J* = 2.0, 1.0 Hz, 3 H), 1.61 (dd, *J* = 1.0, 1.0 Hz, 3 H), 1.66 (ddd, *J* = 7.0, 3.5, 2.0 Hz, 1 H), 2.82-3.06 (m, 2 H), 4.56 (br dd, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.21 (q'), 12.69 (q'), 27.61 (q'), 29.13(q'), 39.89 (t'), 41.85 (s'), 44.42 (d'), 46.19 (t'),

52.95 (d'), 79.75 (d'), 131.07 (s'), 137,70 (s'); exact mass *m/z* calcd for $C_{12}H_{20}O$ 180.1514, found 180.1509. An analytical sample was prepared by Kugelrohr distillation (90-100 °C, 0.6 mm Hg). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.95; H, 11.32.

(1α,3aα,6aα)-(±)-1,3a,4,5,6,6a-Hexahydro-2,3,5,5-tetramethyl-1-pentalenol (120).

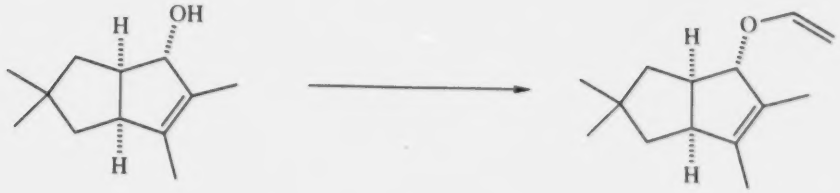


118 **119** **120**

Ph_3P (611.1 mg, 2.66 mmol) and chloroacetic acid (251.4 mg, 2.66 mmol) were added successively to a stirred solution of allylic alcohol **118** (240.1 mg, 1.33 mmol) in dry PhH (10 mL) at room temperature. DEAD (0.42 mL, 2.66 mmol) was added dropwise over *ca.* 3 min, and stirring was continued for 3 h. Evaporation of the solution gave a mixture that contained the desired chloro acetate (**119**). The mixture was dissolved in THF (10 mL plus 5 mL as a rinse) and this solution was added dropwise over *ca.* 5 min to a cooled (0 °C) and stirred suspension of $LiAlH_4$ (303.2 mg, 8.00 mmol) in THF (25 mL). The cooling bath was removed and stirring was continued for 30 min. The mixture was then quenched by successive addition

of water (0.3 mL), aqueous NaOH (3 M, 0.3 mL), and water (0.9 mL). The resulting mixture was stirred for 20 min and then filtered through a pad (2 x 4 cm) of Celite. The pad was washed with EtOAc and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 10% EtOAc-hexane, gave allylic alcohol **120** (138.2 mg, 58%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3309, 3295 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.99 (s, 3 H), 0.99 (d, J = 11.0 Hz, 1 H), 1.05 (dd, J = 11.0, 10.0 Hz, 1 H), 1.40 (d, J = 7.5 Hz, 1 H), 1.58 (ddd, J = 2.0, 1.5, 1.5 Hz, 3 H), 1.62 (ddd, J = 2.0 Hz, 1 H), 1.64 (ddd, J = 2.0, 1.0, 1.0 Hz, 3 H), 1.78 (ddd, J = 12.0, 8.5, 2.0 Hz, 1 H), 2.5 (dddd, J = 12.0, 10.0, 8.0, 2.0 Hz, 1 H), 3.18 (br ddd, J = 8.0, 8.0, 8.0 Hz, 1 H), 4.19 (br d, J = 8.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.41 (q'), 12.86 (q'), 27.30 (q'), 28.71 (q'), 41.47 (s'), 44.82 (t'), 45.87 (t'), 50.95 (d'), 52.76 (d'), 83.38 (d'), 130.38 (s'), 140.68 (s'); exact mass *m/z* calcd for $C_{12}H_{20}O$ 180.1514, found 180.1510. An analytical sample was prepared by crystallization from hexane: mp 38-39 °C. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.10; H, 11.19.

(1α,3aα,6aα)-(±)-1,3a,4,5,6,6a-Hexahydro-1,2,5,5-tetramethyl-1-pentaleneethanol (122). Use of Ethyl Vinyl Ether.



120 **121**

The yield in this experiment was not always reproducible. NaOAc (213.3 mg, 2.60 mmol) and $Hg(OAc)_2$ (414.3 mg, 1.30 mmol) were added to a stirred solution of alcohol **120** (234.5 mg, 1.30 mmol) in freshly distilled ethyl vinyl ether (120 mL). The resulting suspension was refluxed for 72 h and then cooled to room temperature. Anhydrous K_2CO_3 was added, and the excess of ethyl vinyl ether was evaporated. The residue was taken up in 2:3 CH_2Cl_2-hexane and filtered through a pad (2 x 4 cm) of Celite. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 2% EtOAc-hexane, gave the desired vinyl ether (**121**) (210.2 mg, 78%) as a colorless oil containing trace impurities (^{1}H NMR, 200 MHz): FTIR (film) 2951, 2930, 2866, 1644, 1629, 1603, 1463, 1442, 1382, 1366, 1158 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 1.02 (s, 3 H), 1.02 (d, J = 13.0 Hz, 1 H), 1.14 (dd, J = 13.0, 10.0 Hz, 1 H), 1.55-1.64 (m, 6 H), 1.64 (ddd, J = 13.0, 9.0, 2.0 Hz, 1 H), 1.78 (ddd, J = 13.0, 8.0, 2.0 Hz, 1 H), 2.6 (dddd, J = 9.0, 9.0, 8.0, 2.0 Hz, 1 H), 3.2 (br ddd, J = 8.0, 8.0, 8.0

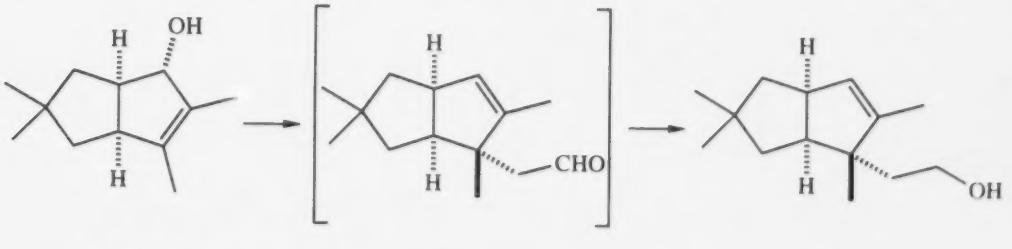
Hz, 1 H), 4.00 (dd, J = 7.0, 1.5 Hz, 1 H), 4.23 (dd, J = 14.0, 1.5 Hz, 1 H), 4.37 (br s, 1 H), 6.41 (ddd, J = 14.0, 7.0, 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.71 (q'), 12.88 (q'), 27.18 (q'), 28.70 (q'), 41.71 (s'), 45.05 (t'), 45.96 (t'), 46.93 (d'), 52.23 (d'), 87.74 (t'), 93.90 (d'), 127.44 (s'), 142.99 (s'), 150.85 (d'); exact mass m/z calcd for $C_{14}H_{22}O$ 206.1671, found 206.1670.

121 **122**

i-Bu_3Al (1.0 M in PhMe, 3.9 mL, 3.9 mmol) was added to a cooled (-78 °C) and stirred solution of vinyl ether **121** (201.0 mg, 0.974 mmol) in CH_2Cl_2 (15 mL). The cold bath was removed and, after 1.5 h, the solution was cooled to -78 °C and quenched by addition of hydrochloric acid (1 M, 2 mL). The resulting mixture was poured into a separatory funnel containing 1 M hydrochloric acid (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 17 cm), using 20% EtOAc-hexane, gave alcohol **122** (186.1 mg, 91%) as a pure (^1H NMR, 200 MHz) colorless oil: FTIR (CH_2Cl_2 cast) 3324 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (s, 3 H), 0.95 (s, 3 H), 1.01 (s, 3 H), 1.04 (dd, J = 13.0, 7.0 Hz, 1 H), 1.27 (dd, J = 2.0,

2.0 Hz, 1 H), 1.32 (d, 1.5 Hz, 1 H), 1.35 (dd, J = 6.0, 6.0 Hz, 1 H), 1.58 (ddd J = 1.5, 1.5, 1.5 Hz, 3 H), 1.61-1.71 (m, 3 H), 2.60 (ddd, J = 11.0, 8.0, 7.0 Hz, 1 H), 2.96-3.14 (m, 1 H), 3.65 (ddd, J = 7.5, 7.0, 6.0 Hz, 2 H), 5.18 (dd, J = 1.5, 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.54 (q'), 21.31 (q'), 27.46 (q'), 29.30 (q'), 40.49 (s'), 43.02 (t'), 44.53 (t'), 46.46 (t'), 47.22 (d'), 48.87 (s'), 51.67 (d'), 60.55 (t'), 129.57 (d'), 143.14 (s'); exact mass *m/z* calcd for $C_{14}H_{24}O$ 208.1827, found 208.1829. An analytical sample was prepared by Kugelrohr distillation (68-70 °C, 1.5 mmHg). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.52; H, 11.68.

(1α,3aα,6aα)-(±)-1,3a,4,5,6,6a-Hexahydro-1,2,5,5-tetramethyl-1-pentaleneethanol (122). Use of Phenyl Vinyl Sulfoxide.



120 **124** **122**

Alcohol **120** (540.8 mg, 3.00 mmol) in THF (5 mL plus 1 mL as a rinse) was added to a stirred suspension of NaH (72.0 mg, 3.00 mmol) in THF (5 mL) at room temperature. Stirring was continued for 30 min, and then a solution of phenyl vinyl sulfoxide (0.53 mL, 4.00 mmol) in THF (2 mL), and a catalytic

amount (1 mg) of KH were added. The mixture was stirred for 4 h, and then quenched by addition of moist EtOAc, followed by water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in decalin (10 mL), and $NaHCO_3$ (10 g) was added. The resulting mixture was heated (150 °C) and stirred for 40 h, and then cooled to room temperature. Water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using first hexane, and then 10% EtOAc-hexane, gave crude (TLC, 20% EtOAc-hexane) aldehyde **124**, which was used without further purification.

All of the crude **124** in THF (3 mL plus 2 mL as a rinse) was added to a stirred and cooled (-78 °C) suspension of $LiAlH_4$ (79.9 mg, 2.00 mmol) in THF (15 mL). The cold bath was removed, the mixture was allowed to warm to room temperature (30 min), and the reaction was quenched by successive addition of water (0.08 mL), aqueous NaOH (3 M, 0.08 mL), and water (0.24 mL). The resulting mixture was stirred for 20 min and then filtered through a pad (3 x 3 cm) of Celite. The pad was washed with EtOAc and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 20% EtOAc-hexane, gave alcohol **122** (453.6 mg, 73%) as a pure (^1H NMR,

200 MHz), colorless oil, spectroscopically identical with material made using ethyl vinyl ether.

(1α,3aα,6aα)-(±)-1-(2-Bromoethyl)-1,3a,4,5,6,6a-hexahydro-1,2,5,5-tetramethylpentalene (125).

122 **125**

Ph_3P (786.9 mg, 3.00 mmol) and CBr_4 (995.0 mg, 3.00 mmol) were added successively to a cooled (0 °C) and stirred solution of alcohol **122** (443.6 mg, 2.13 mmol) in CH_2Cl_2 (40 mL). The cold bath was removed, and after 1.5 h, the mixture was filtered through a pad (3 x 3 cm) of flash chromatography silica gel, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3.5 x 25 cm), using petroleum ether, gave bromide **125** (551.6 mg, 96%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3027, 2952, 2932, 2865, 2857, 1462, 1445, 1381, 1371, 1365 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (s, 3 H), 0.95 (s, 3 H), 1.02 (s, 3 H), 1.04 (dd, J = 13.0, 7.0 Hz, 1 H), 1.20-1.38 (m, 2 H), 1.54 (dd, J = 2.0, 1.0 Hz, 3 H), 1.63 (ddd, J = 13.0, 9.5, 2.0 Hz, 1 H), 1.81-2.06 (m, 2 H), 2.53 (ddd, J = 13.0, 8.0, 7.0 Hz, 1 H), 2.90-3.09 (m, 1 H), 3.17-3.46 (m, 2 H), 5.21 (dd, J = 1.0, 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.44 (q'), 20.72 (q'), 27.46 (q'), 29.27 (q'), 29.99 (t'),

40.56 (s'), 42.99 (t'), 45.47 (t'), 46.40 (t'), 47.31 (d'), 51.15 (d'), 51.21 (s'), 130.15 (d'), 141.18 (s'); exact mass *m/z* calcd for $C_{14}H_{23}Br$ 270.0984, found 270.0982. An analytical sample was prepared by Kugelrohr distillation (82-85 °C, 1.5 mmHg). Anal. Calcd for $C_{14}H_{23}Br$: C, 61.99; H, 8.55; Br, 29.46. Found C, 61.66; H, 8.83; Br, 29.71.

(1α,3aα,6aα)-(±)-1-(3-Butynyl)-1,3a,4,5,6,6a-hexahydro-1,2,5,5-tetramethylpentalene (126).

125 **126**

n-BuLi (1.6 M in hexane, 3.13 mL, 5.00 mmol) was added dropwise over *ca.* 5 min to a cooled (-78 °C) and stirred solution of trimethylsilylacetylene (1.41 mL, 10.0 mmol) in THF (15 mL). After a further 15 min, a solution of bromide **125** (267.0 mg, 0.984 mmol) in THF (5 mL plus 3 mL as a rinse), followed by HMPA (1 mL), were added. The cold bath was removed and stirring was continued for 6 h. Methanolic NaOH (1 M, 15 mL) was added and stirring was continued overnight. The mixture was quenched with water and extracted with hexane. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using petroleum ether, gave enyne **126** (199.6 mg, 94%) as a pure (^1H NMR, 200 MHz),

colorless oil: FTIR (film) 3313, 3027, 2952, 2934, 2867, 2119, 1463, 1447, 1440, 1380, 1374, 1365 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 0.93 (s, 3 H), 1.01 (s, 3 H), 1.02 (dd, *J* = 13.0, 7.5 Hz, 1 H), 1.17-1.33 (m, 2 H), 1.47-1.74 (m, 3 H), 1.53 (dd, *J* = 3.0, 1.5 Hz, 3 H), 1.92 (dd, *J* = 2.5, 2.5 Hz, 1 H), 2.01-2.16 (m, 2 H), 2.52 (ddd, *J* = 10.0, 9.0, 8.0 Hz, 1 H), 2.89-3.08 (m, 1 H), 5.21 (dd, *J* = 1.5, 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.39 (q'), 13.99 (t'), 20.71 (q'), 27.41 (q'), 29.28 (q'), 40.53 (s'), 40.64 (t'), 43.09 (t'), 46.48 (t'), 47.22 (d'), 49.89 (s'), 50.94 (d'), 67.63 (d'), 85.64 (s'), 129.88 (d'), 141.67 (s'); exact mass *m/z* calcd for $C_{16}H_{24}$ 216.1878, found 216.1870. An analytical sample was prepared by Kugelrohr distillation (85-90 °C, 1.7 mm Hg). Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.65; H, 11.12.

(1R*,2R*,6S*,7R*)-(±)-1,4,4,11-Tetramethyl-8-methylenetricyclo[5,3,1,$0^{2,6}$]undecane (127).

126 **127**

Bu_3SnH (0.11 mL, 0.42 mmol) in PhMe (1 mL) was added to a warmed (80 °C) and stirred solution of enyne **126** in PhMe (5 mL). AIBN (3.4 mg, 0.021 mmol) was added, and stirring was continued for 3 h. The mixture was then cooled and

evaporated. Flash chromatography of the residue over silica gel (1.5 x 30 cm), using petroleum ether, gave a mixture (^{1}H NMR, 200 MHz) of olefin **127** and a byproduct (35.4 mg, *ca.* 78%, 5:1 in favor of **127**).

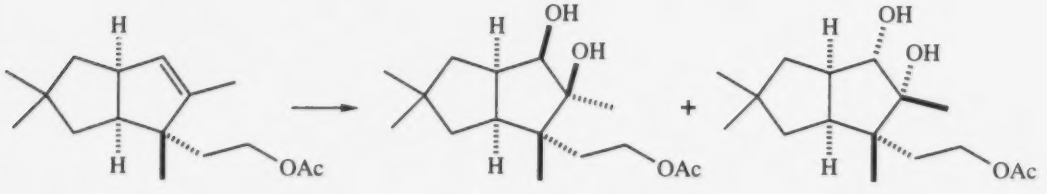
A sample of **127**, containing only trace impurities, was obtained by repeated flash chromatography, in which late fractions were discarded. This material had: FTIR (neat film) 3068, 2950, 2930, 2870, 2857, 1648, 1464, 1438, 1381, 1373, 1365 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 0.75 (d, J = 7.0 Hz, 3 H), 0.76 (s, 3 H), 0.90-1.24 (m, 3 H), 0.92 (s, 3 H), 1.05 (s, 3 H), 1.29-1.86 (m, 4 H), 1.95-2.10 (m, 2 H), 2.15-2.42 (m, 3 H), 4.45 (dd, J = 2.5, 2.5 Hz, 1 H), 4.55 (dd, J = 2.5, 2.5 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 10.06 (q'), 21.03 (q'), 26.44 (q'), 28.75 (q'), 28.91 (t'), 34.46 (t'), 39.24 (d'), 40.38 (s'), 41.70 (s'), 44.31 (t'), 46.34 (d'), 47.65 (t'), 51.92 (d'), 55.68 (d'), 105.93 (t'), 150.66 (s'); exact mass *m/z* calcd for $C_{16}H_{26}$ 218.20344, found 218.20302.

Acetic acid (1α,3aα,6aα)-(±)-2-(1,3a,4,5,6,6a-hexahydro-1,2,5,5-tetramethylpentalen-1-yl)ethyl ester (142).

122 **142**

Pyridine (0.42 mL, 5.2 mmol) and Ac_2O (0.49 mL, 5.2 mmol) were added successively to a stirred solution of alcohol **122** (536.7 mg, 2.58 mmol) in CH_2Cl_2 (6 mL). The solution was stirred for 16 h, then diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 5% EtOAc-hexane, gave ester **142** (619.1 mg, 96%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1743 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.91 (s, 3 H), 0.97 (s, 3 H), 1.01 (s, 3 H), 1.02 (dd, J = 13.0, 7.0 Hz, 1 H), 1.26-1.38 (m, 2 H), 1.55 (dd, J = 2.0, 1.5 Hz, 3 H), 1.55-1.78 (m, 3 H), 1.99 (s, 3 H), 2.61 (ddd, J = 9.0, 8.5, 8.0 Hz, 1 H), 2.93-3.12 (m, 1 H), 3.90-4.10 (m, 2 H), 5.20 (dd, J = 2.0, 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 12.48 (q'), 21.10 (q'), 21.19 (q'), 27.52 (q'), 29.41 (q'), 39.95 (t'), 40.79 (s'), 43.27 (t'), 46.78 (t'), 47.50 (d'), 49.11 (s'), 51.82 (d'), 62.51 (t'), 129.86 (d'), 142.39 (s'), 171.22 (s'); exact mass m/z calcd for $C_{16}H_{26}O_2$ 250.19328, found 250.19268.

Acetic acid (1α,2β,3β,3aα,6aα)- and (1α,2α,3α,3aα,6aα)-(±)-2-(2,3-dihydroxyoctahydro-1,2,5,5-tetramethylpentalen-1-yl)ethyl ester (143a) and (143b).



142 **143a** **143b**

OsO_4 (2.5 w/w% in 2-methyl-2-propanol, 3.80 mL, 0.300 mmol) was added dropwise to a stirred solution of olefin **142** (619.1 mg, 2.47 mmol) in acetone (14 mL) and water (1.4 mL). 4-Methylmorphine *N*-oxide monohydrate (585.8 mg, 5.00 mmol) was added in one portion and stirring was continued for 18 h. The solution was filtered through a pad (3.5 x 6 cm) of Celite on top of a pad (3.5 x 6 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3.5 x 25 cm), using 30% EtOAc-hexane, gave diol **143a** (381.4 mg, 54%) as a pure (^{1}H NMR, 200 MHz), colorless oil and diol **143b** (277.2 mg, 39%) as a pure (^{1}H NMR, 200 MHz), colorless oil. The stereochemical assignments to **143a** and **143b** were made on the basis of coupling constants of the derived ketals **144a** and **144b** (see the next two experiments).

The major diastereomer **143a** had: FTIR (CH_2Cl_2 cast) 3478 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.96 (s, 3 H), 0.98 (s, 3 H), 1.03 (s, 3 H), 1.05 (s, 3 H), 1.18-1.43 (m, 2 H), 1.44

(dd, J = 9.0, 6.0 Hz, 1 H), 1.53-1.73 (m, 3 H), 2.00 (s, 3 H), 2.14 (s, 1 H), 2.21 (d, J = 6.5 Hz, 1 H), 2.46 (ddd, J = 10.0, 10.0, 8.5 Hz, 1 H), 2.76 (dddd, J = 10.0, 10.0, 9.0, 9.0 Hz, 1 H), 3.90 (dd, J = 8.5, 6.5 Hz, 1 H), 4.01-4.23 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 15.67 (q'), 21.19 (q'), 21.85 (q'), 26.77 (q'), 29.13 (q'), 37.77 (t'), 40.47 (t'), 41.19 (s'), 43.58 (t'), 43.81 (d'), 45.22 (s'), 50.10 (d'), 62.53 (t'), 77.90 (d'), 84.39 (s'), 171.22 (s'); exact mass m/z calcd for $C_{16}H_{28}O_4$ 284.19875, found 284.19853.

The minor diastereomer **143b** had: FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.81 (s, 3 H), 0.94 (s, 3 H), 1.03-1.13 (m, 1 H), 1.06 (s, 3 H), 1.10 (s, 3 H), 1.31 (br d, J = 10.0 Hz, 2 H), 1.51-1.68 (m, 1 H), 1.79 (dd, J = 11.5, 8.0 Hz, 1 H), 1.86-2.0 (m, 1 H), 2.0 (s, 3 H), 2.04 (d, J = 7.0 Hz, 1 H), 2.13 (s, 1 H), 2.48 (dddd, J = 10.0, 8.0, 7.5, 7.5 Hz, 1 H), 2.74 (ddd, J = 9.0, 9.0, 8.0 Hz, 1 H), 3.66 (dd, J = 7.0, 7.0 Hz, 1 H), 3.91-4.17 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 20.16 (q'), 20.39 (q'), 21.22 (q'), 27.20 (q'), 29.15 (q'), 35.17 (t'), 42.06 (t'), 44.23 (s'), 45.59 (s'), 46.79 (t'), 49.70 (d', d' overlapping), 62.66 (t'), 83.85 (d'), 86.35 (s'), 171.26 (s'); exact mass m/z calcd for $C_{16}H_{28}O_4$ 284.19875, found 284.19878.

(3aα,3bβ,6aα,7α,7aα)-(±)-2-(1,3-Dioxadecahydro-2,2,5,5,7,7a-hexamethyl-(1*H*)-cyclopenta[a]pentalen-7-yl)ethanol (144a).

143a **144a**

2,2-Dimethoxypropane (1.61 mL, 9.47 mmol) and a solution of PPTS (23.8 mg, 0.0947 mmol) in DMF (2 mL) were added successively to a cooled (0 °C) and stirred solution of diol **143a** (269.2 mg, 0.947 mmol) in DMF (4 mL). The cold bath was removed and stirring was continued overnight. The reaction was quenched by addition of anhydrous $NaHCO_3$, and the mixture was then diluted with EtOAc (40 mL). The organic solution was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (15 mL), and anhydrous K_2CO_3 (1.31 mg, 9.47 mmol) was added in one portion. The resulting mixture was then stirred for 1 h, diluted with water (40 mL), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 30% EtOAc-hexane, gave alcohol **144a** (241.8 mg, 90%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3363 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.95 (s, 6 H), 1.09 (s, 3 H), 1.24-1.41 (m, 3 H), 1.35 (d, J = 1.0

Hz, 3 H), 1.36 (s, 3 H), 1.47 (d, J = 1.0 Hz, 3 H), 1.47-1.76 (m, 4 H), 2.50 (ddd, J = 10.0, 8.5, 8.5 Hz, 1 H), 2.70 (dddd, J = 10.0, 10.0, 7.5, 7.5 Hz, 1 H), 3.44-3.56 (m, 2 H), 4.22 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.87 (q'), 22.87 (q'), 25.85 (q'), 26.52 (q'), 29.06 (q'), 29.42 (q') , 40.55 (t'), 41.41 (t'), 41.70 (t'), 42.16 (s'), 42.87 (d'), 46.68 (s'), 54.97 (d'), 60.50 (t'), 87.90 (d'), 95.14 (s'), 111.76 (s'); exact mass *m/z* calcd for $C_{17}H_{30}O_3$ 282.21948, found 282.21952.

The coupling constant (7.5 Hz) for the doublet at 4.22 ppm in the ^1H NMR spectrum of this compound indicates the stereochemistry shown (H_a and H_b *syn*). The corresponding J value for **144b** (see next experiment) is 2.0 Hz.

(3aβ,3bα,6aα,7α,7aβ)-(±)-2-(1,3-Dioxadecahydro-2,2,5,5,7,7a-hexamethyl-(1*H*)-cyclopenta[a]pentalen-7-yl)ethanol (144b).

143b **144b**

2,2-Dimethoxypropane (1.01 mL, 8.18 mmol) and a solution of PPTS (20.6 mg, 0.0818 mmol) in DMF (2 mL) were added successively to a cooled (0 °C) and stirred solution of diol **143b** (232.7 mg, 0.818 mmol) in DMF (3 mL). The cold bath was

removed and stirring was continued overnight. The mixture was quenched by addition of anhydrous $NaHCO_3$, diluted with EtOAc (35 mL), and washed with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in MeOH (15 mL), and anhydrous K_2CO_3 (1.13 g, 8.18 mmol) was added in one portion. The resulting mixture was stirred for 1 h, diluted with water (35 mL), and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 30% EtOAc-hexane, gave alcohol **144b** (211.6 mg, 92%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3428 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.82 (s, 3 H), 0.94 (s, 3 H), 1.04 (s, 3 H), 1.03-1.41 (m, 3 H), 1.30 (s, 3 H), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.56-1.80 (m, 3 H), 2.09 (t, J = 5.5 Hz, 1 H), 2.59 (dddd, J = 10.0, 10.0, 8.0, 2.0 Hz, 1 H), 2.87 (ddd, J = 10.0, 9.0, 9.0 Hz, 1 H), 3.59 (ddd, J = 6.0, 5.5, 5.5 Hz, 2 H), 4.10 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 21.21 (q'), 21.59 (q'), 28.47 (q'), 29.06 (q'), 29.25 (q'), 29.44 (q'), 41.58 (t'), 41.67 (t'), 41.86 (s'), 47.06 (t'), 48.28 (s'), 49.97 (d'), 51.87 (d'), 59.94 (t'), 92.42 (d'), 97.14 (s'), 110.98 (s'); exact mass *m/z* calcd for $C_{17}H_{30}O_3$ 282.21948, found 282.21984.

The coupling constant (2.0 Hz) for the doublet at 4.22 ppm in the ^1H NMR spectrum of this compound indicates the stereochemistry shown (H_a and H_b *anti*). The corresponding J value for **144a** (see previous experiment) is 7.5 Hz.

(3aα,3bα,6aα,7α,7aα)-(±)-7-(2-Bromoethyl)-1,3-dioxadecahydro-2,2,5,5,7,7a-hexamethyl-(1*H*)-cyclopenta[a]pentalene (145a).

144a **145a**

Ph_3P (566.5 mg, 2.16 mmol) and CBr_4 (716.4 mg, 2.16 mmol) were added successively to a cooled (0 °C) and stirred solution of alcohol **144a** (303.8 mg, 1.08 mmol) in CH_2Cl_2 (30 mL). The cold bath was removed and, after 1.5 h, the mixture was filtered through a pad (3 x 3 cm) of flash chromatography silica gel, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3.5 x 20 cm), using 5% EtOAc-hexane, gave bromide **145a** (339.1 mg, 91%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2985, 2953, 2887, 2869, 1463, 1376, 1205 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.94 (s, 3 H), 0.95 (s, 3 H), 1.09 (s, 3 H), 1.24-1.96 (m, 6 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 1.46 (s, 3 H), 2.46 (dddd, *J* = 10.0, 9.0, 9.0 Hz, 1 H), 2.69 (dddd, *J* = 9.0, 9.0, 7.5, 7.5 Hz, 1 H), 3.25-3.47 (m, 2 H), 4.19 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.38 (q'), 22.80 (q'), 25.94 (q'), 26.47 (q'), 29.00 (q'), 29.33 (q'), 30.76 (t'), 40.40 (t'), 41.72 (t'), 42.20 (s'), 43.05 (d'), 43.93 (t'), 48.97 (s'), 54.47 (d'), 87.89 (d'), 95.03

(s'), 111.66 (s'); exact mass *m/z* calcd for $C_{17}H_{29}{}^{79}BrO_2$ 344.13513, found 344.13509.

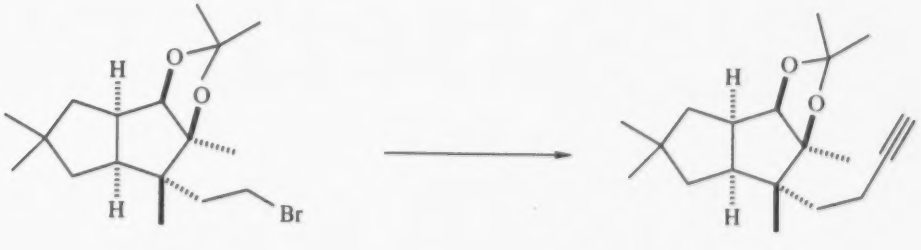
(3aβ,3bα,6aα,7α,7aβ)-(±)-7-(2-Bromoethyl)-1,3-dioxadecahydro-2,2,5,5,7,7a-hexamethyl-(1*H*)-cyclopenta[a]pentalene (145b).

144b **145b**

Ph_3P (351.5 mg, 1.34 mmol) and CBr_4 (444.4 mg, 1.34 mmol) were added successively to a cooled (0 °C) and stirred solution of alcohol **144b** (252.8 mg, 0.895 mmol) in CH_2Cl_2 (30 mL). Stirring was continued at 0 °C for 10 min, the cold bath was then removed and stirring was continued for 1 h. The mixture was filtered through a pad (3 x 3 cm) of flash chromatography silica gel using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3.5 x 20 cm), using 5% EtOAc-hexane, gave bromide **145b** (259.0 mg, 84%) as a pure (TLC), colorless oil. The material decomposes significantly over a day at room temperature, and so it was used immediately for the next step: Compound **145b** has: FTIR (CH_2Cl_2 cast) 2982, 2951, 2867, 1463, 1378, 1367, 1228 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.84 (s, 3 H), 0.93 (s, 3 H), 1.03-1.20 (m, 1 H), 1.05 (s, 3 H), 1.25-1.47 (m, 2 H),

1.29 (s, 3 H), 1.39 (d, J = 0.5 Hz, 3 H), 1.43 (s, 3 H), 1.70 (ddd, J 12.0, 8.0, 1.0 Hz, 1 H), 1.98-2.17 (m, 2 H), 2.64 (dddd, J = 10.0, 10.0, 8.0, 2.0 Hz, 1 H), 2.79 (ddd, J = 10.0, 9.0, 9.0 Hz, 1 H), 3.28-3.56 (m, 2 H), 4.07 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.60 (q'), 22.28 (q'), 28.23 (q'), 28.58 (q'), 28.94 (q'), 29.25 (q'), 31.25 (t'), 41.84 (s'), 42.42 (t'), 43.53 (t'), 47.06 (t'), 49.33 (d'), 50.11 (s'), 52.59 (d'), 92.69 (d'), 96.59 (s'), 111.03 (s'); exact mass *m/z* calcd for $C_{17}H_{29}{}^{79}BrO_2$ 344.13513, found 344.13497.

(3aα,3bα,6aα,7α,7aα)-(±)-7-(3-Butynyl)-1,3-dioxadecahydro-2,2,5,5,7,7a-hexamethyl-(1*H*)-cyclopenta[a]pentalene (146a).



145a **146a**

n-BuLi (1.6 M in hexane, 1.44 mL, 2.30 mmol) was added dropwise over *ca.* 5 min to a cooled (-78 °C) and stirred solution of trimethylsilylacetylene (0.93 mL, 5.70 mmol) in THF (10 mL). After a further 15 min, a solution of bromide **145a** (196.7 mg, 0.570 mmol) in THF (5 mL plus 2 mL as a rinse), followed by HMPA (1 mL), were added. The cold bath was removed and stirring at room temperature was continued

for 6 h. Methanolic NaOH (1 M, 15 mL) was added and stirring was continued overnight. The mixture was quenched with water and extracted with hexane. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm) using 5% EtOAc-hexane, gave acetylene **146a** (136.4 mg, 82%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3312, 2986, 2954, 2886, 2868, 2118, 1464, 1447, 1375, 1204, 1093 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.92 (s, 3 H), 0.95 (s, 3 H), 1.08 (s, 3 H), 1.21-1.75 (m, 6 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 1.46 (s, 3 H), 1.95 (dd, J = 2.5, 2.5 Hz, 1 H), 1.98-2.26 (m, 2 H), 2.45 (ddd, J = 10.0, 9.0, 9.0 Hz, 1 H), 2.66 (dddd, J = 9.0, 9.0, 9.0, 7.5 Hz, 1 H), 4.18 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.94 (t'), 19.11 (q'), 22.73 (q'), 26.11 (q'), 26.60 (q'), 29.02 (q'), 29.42 (q'), 39.06 (t'), 40.32 (t'), 41.94 (t'), 42.11 (s'), 43.12 (d'), 47.52 (s'), 54.36 (d'), 67.95 (d'), 85.69 (s'), 88.19 (d'), 95.24 (s'), 111.39 (s'); exact mass m/z calcd for $C_{19}H_{30}O_2$ 290.22458, found 290.22499.

(3aβ,3bα,6aα,7α,7aβ)-(±)-7-(3-Butynyl)-1,3-dioxadecahydro-2,2,5,5,7,7a-hexamethyl-(1*H*)-cyclopenta[a]pentalene (146b).

145b **146b**

n-BuLi (1.6 M in hexane, 1.88 mL, 1.88 mL, 3.00 mL) was added dropwise over *ca.* 5 min to a cooled (-78 °C) and stirred solution of trimethylsilylacetylene (1.09 mL, 7.50 mmol) in THF (12 mL). After a further 15 min, a solution of bromide **145b** (259.0 mg, 0.750 mmol) in THF (5 mL plus 3 mL as a rinse), followed by HMPA (1 mL), were added. The cold bath was removed and stirring at room temperature was continued for 6 h. Methanolic NaOH (1 M, 20 mL) was added and stirring was continued overnight. The mixture was quenched with water and extracted with hexane. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 5% EtOAc-hexane, gave acetylene **146b** (183.6 mg, 84%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3312, 2983, 2952, 2866, 2118, 1461, 1378, 1367, 1230, 1052 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.80 (s, 3 H), 0.93 (s, 3 H), 1.05 (s, 3 H), 1.12 (dd, J = 12.0, 12.0 Hz, 1 H), 1.29 (s, 3 H), 1.32-1.51 (m, 1 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.55-1.90 (m, 4

H), 1.95 (dd, J = 2.5, 2.5 Hz, 1 H), 1.96-2.28 (m, 2 H), 2.59 (dddd, J = 8.0, 8.0, 8.0, 2.0 Hz, 1 H), 2.77 (ddd, J = 10.0, 10.0, 8.0 Hz, 1 H), 4.07 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.75 (t'), 19.52 (q'), 22.03 (q'), 28.32 (q'), 28.65 (q'), 29.18 (q'), 29.26 (q'), 38.21 (t'), 41.91 (s'), 42.48 (t'), 47.07 (t'), 48.70 (s'), 49.65 (d'), 52.24 (d'), 67.84 (d'), 85.94 (s'), 92.56 (d'), 96.93 (s'), 110.86 (s'); exact mass *m/z* calcd for $C_{19}H_{30}O_2$ 290.22458, found 290.22472.

(1α,2α,3β,3aβ,6aβ)-(±)-3-(3-Butynyl)octahydro-2,3,5,5-tetramethyl-1,2-pentalenediol (147a).

146a **147a**

Acetonide **146a** (95.9 mg, 0.330 mmol) was dissolved in a solution of I_2 (125.6 mg, 0.495 mmol) in MeOH (12.5 mL). The mixture was stirred for 6 h and then quenched with $Na_2S_2O_3$, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave diol **147a** (69.4 mg, 84%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3417, 3310, 2954, 2930, 2865, 2117, 1464, 1445, 1415 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.91 (s, 6 H),

1.05 (s, 3 H), 1.09 (s, 3 H), 1.18-1.44 (m, 3 H), 1.47-1.73 (m, 3 H), 1.97 (dd, J = 2.5, 2.5 Hz, 1 H), 2.04-2.29 (m, 3 H), 2.06 (s, 1 H), 2.43 (ddd, J = 10.0, 10.0, 8.0 Hz, 1 H), 2.74 (dddd, J = 10.0, 10.0, 10.0, 9.0 Hz, 1 H), 3.92 (dd, J = 9.0, 6.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.51 (t'), 15.03 (q'), 21.73 (q'), 26.73 (q'), 29.14 (q'), 38.70 (t'), 40.52 (t'), 41.17 (s'), 43.71 (d'), 43.75 (t'), 46.05 (s'), 49.39 (d'), 68.04 (d'), 77.87 (d'), 84.48 (s'), 85.69 (s'); exact mass m/z calcd for $C_{16}H_{26}O_2$ 250.19328, found 250.19331.

(1α,2α,3α,3aα,6aα)-(±)-3-(3-Butynyl)octahydro-2,3,5,5-tetramethyl-1,2-pentalenediol (147b).

146b **147b**

Acetonide **146b** (107.7 mg, 0.371 mmol) was dissolved in a solution of I_2 (141.2 mg, 0.557 mmol) in MeOH (14.1 mL). The mixture was stirred for 5 h, and then quenched with $Na_2S_2O_3$, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave diol **147b** (64.3 mg, 69%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3419, 3311, 2950, 2865, 2117, 1463, 1447

cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.77 (s, 3 H), 0.94 (s, 3 H), 1.02-1.16 (m, 1 H), 1.07 (s, 3 H), 1.10 (s, 3 H), 1.29 (d, *J* = 9.5 Hz, 2 H), 1.43-1.60 (m, 2 H), 1.73 (dd, *J* = 12.0, 8.0 Hz, 1 H), 1.87 (dd, *J* = 11.0, 5.5 Hz, 1 H), 1.94-2.24 (m, 4 H), 2.35-2.77 (m, 2 H), 3.65 (dd, *J* = 7.0, 7.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.48 (t'), 19.75 (q'), 20.15 (q'), 27.16 (q'), 29.13 (q'), 36.12 (t'), 42.39 (t'), 44.37 (s'), 46.50 (s'), 46.73 (t'), 49.49 (d'), 49.71 (d'), 67.90 (d'), 84.01 (d'), 85.86 (s'), 86.29 (s'); exact mass *m/z* calcd for $C_{16}H_{26}O_2$ 250.19328, found 250.19314.

(3aα,3bα,6aα,7α,7aα)-(±)-7-(3-Butynyl)-1,3-dioxadecahydro-2,2,5,5,7,7a-tetramethyl-(1*H*)-cyclopenta[a]pentalene-2-thione (141a).

147a **141a**

DMAP (146.6 mg, 1.20 mmol) and $CSCl_2$ (45 μL, 0.60 mmol) were added successively to a cooled (0 °C) and stirred solution of diol **147a** (48.7 mg, 0.195 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 2 h, and then quenched with flash chromatography silica gel. The resulting mixture was filtered through a pad (2 x 3 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and

flash chromatography of the residue over silica gel (1.0 x 20 cm), using 15% EtOAc-hexane, gave thiocarbonate **141a** (47.3 mg, 83%) as a pure (^{1}H NMR, 200 MHz), white solid: mp 94-95 °C; FTIR (CH_2Cl_2 cast) 3292, 2954, 2884, 2868, 1463, 1457, 1349, 1337, 1302, 1282 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.96 (s, 3 H), 1.07 (s, 3 H), 1.08 (s, 3 H), 1.25-1.77 (m, 6 H), 1.43 (s, 3 H), 2.03 (dd, *J* = 2.5, 2.5 Hz, 1 H), 2.08-2.39 (m, 2 H), 2.63-2.95 (m, 2 H), 4.78 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.58 (t'), 15.96 (q'), 19.52 (q'), 28.49 (q'), 29.51 (q'), 37.95 (t'), 38.92 (t'), 40.95 (s'), 43.17 (t'), 44.80 (d'), 47.76 (s'), 52.33 (d'), 68.93 (d'), 84.20 (s'), 92.29 (d'), 105.01 (s') 190.93 (s'); exact mass *m/z* calcd for $C_{17}H_{24}O_2S$ 292.14969, found 294.14920.

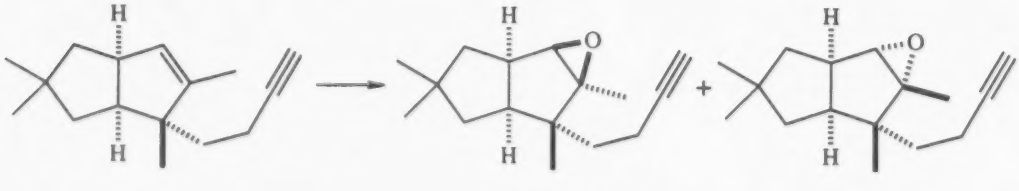
(3aβ,3bα,6aα,7α,7aβ)-(±)-7-(3-Butynyl)-1,3-dioxadecahydro-2,2,5,5,7,7a-tetramethyl-(1*H*)-cyclopenta[a]pentalene-2-thione (141b).

147b **141b**

DMAP (98.0 mg, 0.720 mmol) and $CSCl_2$ (27 μL, 0.360 mmol) were added successively to a cooled (0 °C) and stirred solution of diol **147b** (30.2 mg, 0.121 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 45 min, and then quenched with

flash chromatography silica gel. The resulting mixture was filtered through a pad (2 x 3 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.0 x 20 cm), using 15% EtOAc-hexane, gave thiocarbonate **141b** (31.8 mg, 90%) as a pure (^{1}H NMR, 200 MHz), white solid: FTIR (CH_2Cl_2 cast) 3291, 2954, 2867, 2118, 1460, 1431, 1327, 1310, 1298 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.90 (s, 3 H), 0.96 (s, 3 H), 1.07 (s, 3 H), 1.14-1.29 (m, 1 H), 1.34-1.97 (m, 5 H), 1.46 (s, 3 H), 2.00 (dd, *J* = 2.5, 2.5 Hz, 1 H), 2.01-2.31 (m, 2 H), 2.68-2.92 (m, 2 H), 4.63 (d, *J* = 2 Hz, 1 H); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 14.43 (t'), 18.94 (q'), 19.55 (q'), 28.44 (q'), 28.97 (q'), 36.63 (t'), 42.06 (t'), 42.56 (s'), 45.71 (t'), 49.15 (s'), 49.90 (d'), 51.62 (d'), 68.60 (d'), 84.52 (s'), 94.67 (d'), 106.61 (s'), 191.46 (s'); exact mass *m/z* calcd for $C_{17}H_{24}O_2S$ 292.14969, found 292.14972.

(1aα,2α,2aα,5aα)- and (1aα,2β,2aβ,5aβ)-(±)-2-(3-Butynyl)-1a,2,4,4-tetramethyloctahydropentaleno[1,2-b]oxirene (149a) and (149b).



126 **149a** **149b**

$NaH_2PO_4.H_2O$ (567.8 mg, 4.00 mmol) and MCPBA (552.2 mg, 3.20 mmol) were added to a cooled (0 °C) and stirred solution

of enyne **126** (347.9 mg, 1.61 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred for 3 h, and then the cold bath was removed. Additional CH_2Cl_2 (40 mL) was added and the organic layer was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 5% EtOAc-hexane, gave epoxide **149a** (281.6 mg, 75%) as a pure (^1H NMR, 200 MHz), colorless oil and then epoxide **149b** (95.2 mg, 25%) as a white solid containing trace aromatic impurities (^1H NMR, 200 MHz). The stereochemical assignments to **149a** and **149b** were made on the basis of NOE measurements on the derived ketone **155b** (see later).

The major diastereomer **149a** had: FTIR (CH_2Cl_2 cast) 3312, 2953, 2935, 2863, 2119, 1773, 1462, 1442, 1417, 1374, 1366 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.86 (s, 3 H), 0.95 (s, 3 H), 1.02 (s, 3 H), 1.12 (ddd, *J* = 11.0, 8.0, 1.5 Hz, 1 H), 1.25 (s, 3 H), 1.29-1.69 (m, 5 H), 1.98 (dd, *J* = 2.5, 2.5 Hz, 1 H), 2.03-2.30 (m, 2 H), 2.34 (ddd, *J* = 12.0, 9.0, 7.5 Hz, 1 H), 2.55 (dddd, *J* = 9.0, 7.5, 7.5, 2.0 Hz, 1 H), 3.09 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.12 (t'), 14.22 (q'), 17.23 (q'), 27.45 (q'), 29.09 (q'), 40.19 (t'), 41.44 (t'), 41.76 (s'), 43.33 (d'), 44.80 (s' and t' overlapping), 50.42 (d'), 68.16 (d'), 68.86 (d'), 73.07 (s'), 85.18 (s'); exact mass *m/z* calcd for $C_{16}H_{24}O$ 232.18270, found 232.18325.

The minor diastereomer **149b** had: FTIR (CH_2Cl_2 cast) 3311, 2953, 2933, 2865, 2118, 1772, 1468, 1428, 1419, 1383, 1374, 1366 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.89 (s, 3 H),

0.95 (s, 3 H), 1.04 (s, 3 H), 1.06 (dd, J = 12.0, 12.0 Hz, 1 H), 1.29 (s, 3 H), 1.33-1.77 (m, 5 H), 1.94-2.27 (m, 3 H), 1.95 (dd, J = 2.5, 2.5 Hz, 1 H), 2.73 (ddd, J = 12.0, 9.0, 7.5 Hz, 1 H), 3.12 (s, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.49 (t'), 15.16 (q'), 21.11 (q'), 28.90 (q'), 29.36 (q'), 37.77 (t'), 41.76 (t'), 42.09 (s'), 43.18 (t'), 44.32 (s'), 46.75 (d'), 50.30 (d'), 67.04 (d'), 67.96 (d'), 71.65 (s'), 85.55 (s'); exact mass m/z calcd for $C_{16}H_{24}O$ 232.18270, found 232.18129.

(3aα,3bβ,6aβ,7α,7aα)-(±)-Decahydro-3a,5,5,7a-tetramethyl-1-methylene-(1*H*)-cyclopenta[a]pentalen-7-ol (152a).

149a **152a**

$TiCp_2Cl$ (939.6 mg, 4.40 mmol) in THF (44 mL) was added dropwise over *ca.* 5 min to a stirred solution of epoxide **149a** (466.3 mg, 2.01 mmol) in THF (30 mL). Stirring was continued overnight, and then the mixture was quenched by addition of 10% H_2SO_4 (100 mL). The aqueous phase was extracted with EtOAc, and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 5% EtOAc-hexane, gave alcohol **152a**

(387.6 mg, 82%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3491 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.92 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.07 (s, 3 H), 1.22-1.66 (m, 7 H), 2.27-2.57 (m, 3 H), 2.78 (dddd *J* = 9.0, 7.0, 5.0, 5.0 Hz, 1 H), 3.84 (dd, *J* = 7.0, 5.0 Hz, 1 H), 4.74 (ddd, *J* = 2.5, 2.5, 1.0 Hz, 1 H), 4.84 (ddd, *J* = 2.5, 2.5, 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 16.90 (q'), 20.02 (q'), 27.42 (q'), 29.37 (q'), 30.66 (t'), 40.04 (t'), 40.28 (t'), 41.64 (s'), 43.96 (t'), 46.64 (d'), 51.78 (s'), 53.17 (d'), 61.14 (s'), 81.41 (d'), 104.77 (t'), 162.40 (s'); exact mass *m/z* calcd for $C_{16}H_{26}O$ 234.19836, found 234.19762. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.98; H, 11.37.

(3aα,3bβ,6aβ,7β,7aα)-(±)-Decahydro-3a,5,5,7a-tetramethyl-1-methylene-(1*H*)-cyclopenta[a]pentalen-7-ol (152b).

149b **152b**

$TiCp_2Cl$ (140.9 mg, 0.660 mmol) in THF (6.6 mL) was added dropwise over *ca.* 4 min to a stirred solution of epoxide **149b** (75.3 mg, 0.324 mmol) in THF (6 mL). Stirring was continued for 1.5 h, and then the mixture was quenched by addition of 10% H_2SO_4 (12 mL). The aqueous phase was extracted with

EtOAc, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 5% EtOAc-hexane, gave alcohol **152b** (61.7 mg, 81%) as a pure (^1H NMR, 200 MHz), white solid: FTIR (CH_2Cl_2 cast) 3441 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.90 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.07 (s, 3 H), 1.24-1.56 (m, 5 H), 1.56-1.76 (m, 2 H), 2.04 (dddd, J = 9.0, 9.0, 8.0, 5.5 Hz, 1 H), 2.21-2.50 (m, 3 H), 3.36 (dd, J = 9.0, 9.0 Hz, 1 H), 4.80 (ddd, J = 1.5, 1.0, 1.0 Hz, 1 H), 5.04 (ddd, J = 1.5, 1.0, 1.0 Hz, 1 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 20.32 (q'), 20.84 (q'), 27.67 (q'), 29.54 (q'), 33.17 (t'), 41.30 (s'), 41.47 (t'), 43.69 (t'), 45.30 (t'), 50.40 (s'), 50.67 (d'), 52.13 (d'), 59.23 (s'), 87.60 (d'), 106.91 (t'), 158.90 (s'); exact mass *m/z* calcd for $C_{16}H_{26}O$ 234.19836, found 234.19728. An analytical sample was prepared by crystallization from hexane: mp 50-52 °C. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.88; H, 11.31.

Thiocarbonic acid *O*-phenyl *O*-[(3aα,3bβ,6aβ,7α,7aα)-(±)-decahydro-3a,5,5,7a-tetramethyl-1-methylene-(1H)-cyclopenta[a]pentalen-7-yl] ester (153a).

152a **153a**

Pyridine (100 mL, 1.24 mmol) and phenyl chlorothionoformate (86 mL, 0.62 mmol) were added successively to a stirred solution of alcohol **152a** (36.0 mg, 0.154 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 16 h. The mixture was quenched by addition of water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 2% EtOAc-hexane, gave thionocarbonate **153a** (40.6 mg, 71%) as a pure (^1H NMR, 200 MHz), white solid: mp 60-61 °C; FTIR (CH_2Cl_2 cast) 2952, 2866, 1593, 1490, 1465, 1457, 1382, 1365, 1357, 1301, 1281, 1254, 1243, 1200 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.85 (s, 3 H), 0.93 (s, 3 H), 1.01 (s, 3 H), 1.09 (s, 3 H), 1.24-1.72 (m, 6 H), 2.30-2.65 (m, 3 H), 3.02 (dddd, J = 9.5, 9.5, 8.0, 6.5 Hz, 1 H), 4.91 (dd, J = 2.5, 2.5 Hz, 1 H), 4.97 (dd, J = 2.5, 2.5 Hz, 1 H), 5.52 (d, J = 6.5 Hz, 1 H), 7,06-7.17 (m, 2 H), 7.24-7.49 (m, 3 H); ^{13}C NMR

(75.5 MHz, CD_2Cl_2) δ 18.31 (q'), 19.34 (q'), 27.58 (q'), 29.39 (q'), 30.54 (t'), 39.95 (t'), 40.13 (t'), 42.12 (s'), 43.27 (t'), 45.93 (d'), 52.15 (s'), 53.49 (d'), 61.50 (s'), 95.63 (d'), 106.92 (t'), 122.36 (d'), 126.82 (d'), 129.90 (d'), 153.78 (s'), 160.57 (s'), 195.20 (s'); exact mass *m/z* calcd for $C_{23}H_{30}O_2S$ 370.19666, found 370.19644.

Thiocarbonic acid *O*-phenyl *O*-[(3aα,3bβ,6aβ,7β,7aα)-(±)-decahydro-3a,5,5,7a-tetramethyl-1-methylene-(1*H*)-cyclopenta[a]pentalen-7-yl] ester (153b).

152b **153b**

Pyridine (73 μL, 0.90 mmol) and phenyl chlorothionoformate (62 μL, 0.45 mmol) were added successively to a stirred solution of alcohol **152b** (21.0 mg, 0.0895 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 7 h. The mixture was then quenched by addition of water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 2% EtOAc-hexane, gave thionocarbonate **153b** (21.6 mg, 65%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2951, 2864, 1490, 1465, 1457, 1368, 1289, 1199 cm^{-1}; ^1H

NMR (200 MHz, CD_2Cl_2) δ 0.91 (s, 3 H), 0.92 (s, 3 H), 1.10 (s, 3 H), 1.17 (s, 3 H), 1.38-1.65 (m, 4 H), 1.68 (dd, *J* = 12.0, 8.0 Hz, 1 H), 1.88 (ddd, *J* = 12.0, 9.0, 1.5 Hz, 1 H), 2.26-2.39 (m, 2 H),.2.67 (ddd, *J* = 20.0, 10.0, 8.0 Hz, 1 H), 2.80 (dddd, *J* = 9.0, 9.0, 8.5, 4.5 Hz, 1 H), 4.88 (ddd, *J* = 2.5, 2.5, 0.5 Hz, 1 H), 4.99 (ddd, *J* = 2.5, 2.5, 0.5 Hz, 1 H), 5.33 (d, *J* = 4.5 Hz, 1 H), 7.03-7.12 (m, 2 H), 7.23-7.47 (m, 3 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.20 (q'), 21.66 (q'), 26.86 (q'), 29.34 (q'), 31.78 (t'), 40.02 (t'), 42.00 (s'), 43.82 (t'), 46.99 (t'), 49.41 (d'), 52.77 (d'), 53.08 (s') 60.88 (s'), 100.43 (d'), 108.10 (t'), 122.40 (d'), 126.69 (d'), 129.79 (d'), 153.84 (s'), 157.43 (s'), 195.13 (s'); exact mass *m/z* calcd for $C_{23}H_{30}O_2S$ 370.19666, found 370.19568.

(1R*,2R*,6S*,7R*)-(±)-1,4,4,11-Tetramethyl-8-methylenetricyclo[5,3,1,$0^{2,6}$]undecane (127) from (153a).

153a **127**

Bu_3SnH (93 μL, 0.34 mmol) in PhH (1 mL) was added to a warmed (80 °C) and stirred solution of thionocarbonate **153a** (63.7 mg, 0.172 mmol) in PhH (6 mL). AIBN (5.6 mg, 0.034

mmol) was added and stirring was continued for 2 h. The mixture was then cooled and evaporated. Flash chromatography of the residue over silica gel (1.0 x 25 cm), using petroleum ether, gave a mixture (^{1}H NMR, 200 MHz) of olefin **127** and an isomeric byproduct (30.5 mg, 81%, 10:1 in favor of **127**). See above for spectral data of **127**.

(1R*,2R*,6S*,7R*)-(±)-1,4,4,11-Tetramethyl-8-methylenetricyclo[5,3,1,0^{2,6}]undecane (127) from (153b).

153b **127**

Bu_3SnH (59 µL, 0.22 mmol) in PhH (1 mL) was added to a warmed (80 °C) and stirred solution of thionocarbonate **153b** (40.3 mg, 0.109 mmol) in PhH (4 mL). AIBN (3.6 mg, 0.022 mmol) was added and stirring was continued for 2 h. The mixture was then cooled and evaporated. Flash chromatography of the residue over silica gel (1.0 x 25 cm), using petroleum ether, gave a mixture (^{1}H NMR, 200 MHz) of olefin **127** and an isomeric byproduct (16.2 mg, 65%, 10:1 in favor of **127**). See above for spectral data of **127**.

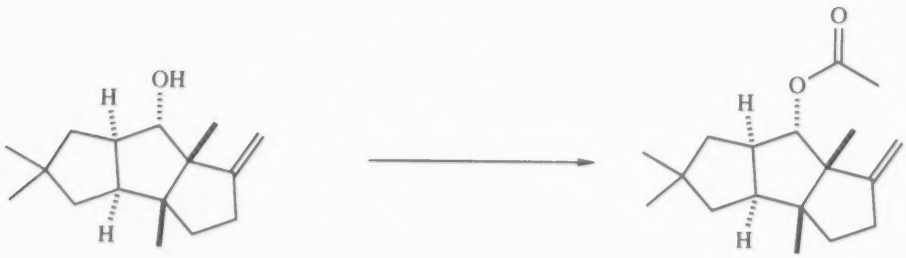
Acetic acid (3aα,3bβ,6aβ,7α,7aα)-(±)-decahydro-3a,5,5,7a-tetramethyl-1-methylene-(1*H*)-cyclopenta[a]pentalen-7-yl ester (154a).

152a **154a**

Pyridine (97 μL, 1.2 mmol), Ac_2O (0.11 mL, 1.2 mmol), AcCl (85 μL, 1.2 mmol), and DMAP (8.5 mg, 0.070 mmol) were added successively to a stirred solution of alcohol **152a** (76.7 mg, 0.328 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred and refluxed for 1 h, allowed to cool to room temperature, diluted with EtOAc (30 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 5% EtOAc-hexane, gave ester **154a** (85.1 mg, 95%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1740 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.91 (s, 3 H), 0.95 (s, 6 H), 1.05 (s, 3 H), 1.14-1.74 (m, 6 H), 2.06 (s, 3 H), 2.27-2.61 (m, 3 H), 2.83 (dddd J = 10.0, 8.0, 8.0, 6.5 Hz, 1 H), 4.84 (dd, J = 2.5, 2.5 Hz, 1 H), 4.90 (ddd, J = 2.5, 2.5, 1.0 Hz, 1 H), 4.95 (d, J = 6.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 18.20 (q'), 20.13 (q'), 21.18 (q'), 27.71 (q'), 29.55 (q'), 30.72 (t'), 40.12 (t'), 40.23 (t'), 41.93 (s'),

43.55 (t'), 45.85 (d'), 52.00 (s'), 53.71 (d'), 60.71 (s'), 84.37 (d'), 106.16 (t'), 161.26 (s'), 170.73 (s'); exact mass *m/z* calcd for $C_{18}H_{28}O_2$ 276.20892, found 276.20853.

Acetic acid (3aα,3bβ,6aβ,7β,7aα)-(±)-decahydro-3a,5,5,7a-tetramethyl-1-methylene-(1*H*)-cyclopenta[a]pentalen-7-yl ester (154b).



152b **154b**

Pyridine (49 μL, 0.60 mmol), Ac_2O (57 μL, 0.60 mmol), AcCl (43 μL, 0.60 mmol), and DMAP (6.1 mg, 0.050 mmol) were added successively to a stirred solution of alcohol **152b** (66.5 mg, 0.284 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 1.5 h, diluted with EtOAc (30 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 5% EtOAc-hexane, gave ester **154b** (74.6 mg, 95%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1739 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.89 (s, 3 H), 0.91 (s, 3 H), 1.03 (s, 3 H), 1.07 (s, 3 H), 1.24-1.52 (m, 3 H), 1.54 (d, *J* = 4.0 Hz, 1 H), 1.61-1.77 (m, 2 H), 1.99 (s, 3 H), 2.24-2.63 (m, 4 H), 4.75-4.85 (m, 2 H), 4.94

(ddd, J = 2.0, 2.0, 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.89 (q'), 21.46 (q'), 21.63 (q'), 27.22 (q'), 29.50 (q'), 32.27 (t'), 40.15 (t'), 42.19 (s'), 43.58 (t'), 46.47 (t'), 48.70 (d'), 52.43 (d'), 52.48 (s'), 59.87 (s'), 88.98 (d'), 107.56 (t'), 158.19 (s'), 170.71 (s'); exact mass m/z calcd for $C_{18}H_{28}O_2$ 276.20892, found 276.20806.

(3aα,3bβ,6aβ,7α,7aα)-(±)-Decahydro-7-hydroxy-3a,5,5,7a-tetramethylcyclopenta[e]pentalen-1-one (155a).

154a **155a**

OsO_4 (2.5 w/w% in 2-methyl-2-propanol, 1.27 mL, 0.100 mmol) was added dropwise to a stirred solution of olefinic acetate **154a** (180.3 mg, 0.652 mmol) in acetone (5 mL) and water (0.5 mL). 4-Methylmorpholine *N*-oxide monohydrate (210.9 mg, 1.80 mmol) was added in one portion, and stirring was continued for 24 h. The mixture was filtered through a pad (1.5 x 6 cm) of Celite on top of a pad (1.5 x 7 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 50% EtOAc-hexane, gave the

desired diols (173.1 mg, 85%) as a mixture (TLC) of diastereomers, which was used without further purification.

K_2CO_3 (414.6 mg, 3.00 mmol) was added to a stirred solution of the above diols in MeOH (8 mL), and stirring was continued for 2 h. The MeOH was evaporated, the flask was flushed with argon, and CH_2Cl_2 (8 mL) was added. The mixture was cooled (0 °C) and $Pb(OAc)_4$ (532.0 mg, 1.20 mmol) was added. The resulting mixture was stirred for 15 min, the cold bath was removed, and stirring was continued for 20 min. The mixture was then filtered through a pad (2 x 3 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave ketone **155a** (123.6 mg, 80% from **154a**) as a pure (^{1}H NMR, 200 MHz), white solid: FTIR (CH_2Cl_2 cast) 1728 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.93 (s, 3 H), 0.97 (s, 3 H), 0.98 (s, 3 H), 1.08 (s, 3 H), 1.25-1.85 (m, 7 H), 2.13-2.48 (m, 2 H), 2.51 (ddd, J = 10.0, 10.0, 9.5 Hz, 1 H), 2.77 (dddd, J = 10.0, 10.0, 9.5, 7.5 Hz, 1 H), 4.03 (dd, J = 7.5, 5.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 12.07 (q'), 19.89 (q'), 26.99 (q'), 29.20 (q'), 35.51 (t'), 40.16 (t', t' overlapping), 41.65 (s'), 43.83 (t'), 47.67 (d'), 49.89 (s'), 53.79 (d'), 65.04 (s'), 77.00 (d'), 222.72 (s'); exact mass m/z calcd for $C_{15}H_{24}O_2$ 236.17763, found 236.17668. An analytical sample was prepared by crystallization from hexane: mp 81-82 °C. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.08; H, 10.52.

(3aα,3bβ,6aβ,7β,7aα)-(±)-Decahydro-7-hydroxy-3a,5,5,7a-tetramethylcyclopenta[e]pentalen-1-one (155b).

154b **155b**

OsO_4 (2.5 w/w% in 2-methyl-2-propanol, 0.70 mL, 0.055 mmol) was added dropwise to a stirred solution of olefinic acetate **154b** (99.3 mg, 0.359 mmol) in acetone (3 mL) and water (0.25 mL). 4-Methylmorpholine *N*-oxide monohydrate (117.2 mg, 1.00 mmol) was added in one portion and stirring was continued for 24 h. The mixture was filtered through a pad (1.5 x 6 cm) of Celite on top of a pad (1.5 x 7 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 50% EtOAc-hexane, gave the desired diols (95.8 mg, 86%) as a mixture (TLC) of diastereomers, which was used without further purification.

K_2CO_3 (248.8 mg, 1.80 mmol) was added to a stirred solution of the above diols in MeOH (5 mL), and stirring was continued for 2 h. The MeOH was evaporated, the flask was flushed with argon, and CH_2Cl_2 (5 mL) was added. The mixture was cooled (0 °C) and $Pb(OAc)_4$ (310.4 mg, 0.700 mmol) was

added. The resulting mixture was stirred for 15 min, the cold bath was removed, and stirring was continued for 20 min. The mixture was then filtered through a pad (2 x 3 cm) of flash chromatography silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave ketone **155b** (63.8 mg, 75% from **154b**) as a pure (^{1}H NMR, 200 MHz), white solid: FTIR (CH_2Cl_2 cast) 1716 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.90 (s, 3 H), 0.96 (s, 3 H), 1.00 (s, 3 H), 1.06 (s, 3 H), 1.22 (dd, J = 10.0, 7.0 Hz, 1 H), 1.30-1.48 (m, 2 H), 1.59-2.01 (m, 3 H), 2.11-2.44 (m, 3 H), 2.55 (ddd, J = 11.0, 11.0, 8.5 Hz, 1 H), 2.88 (d, J = 8.5 Hz, 1 H), 3.54 (dd, J = 8.5, 8.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 16.03 (q'), 20.29 (q'), 27.32 (q'), 29.45 (q'), 35.57 (t'), 37.20 (t'), 42.78 (s'), 43.18 (t'), 46.79 (t'), 48.76 (s'), 51.73 (d'), 52.26 (d'), 62.98 (s'), 88.63 (d'), 227.40 (s'); exact mass *m/z* calcd for $C_{15}H_{24}O_2$ 236.17763, found 236.17678. An analytical sample was prepared by crystallization from hexane: mp 92-93 °C. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.91; H, 10.04.

Irradiation of the C(7)H signal in the proton NMR spectrum caused an enhancement of 8% in the signal intensity of one of the C(6) hydrogens, as expected on the basis of the stereochemistry assigned to **155b**.

Thiocarbonic acid *O*-Phenyl *O*-[(3aα,3bβ,6aβ,7α,7aα)-(±)-decahydro-3a,5,5,7a-tetramethyl-1-oxo-(1*H*)-cyclopenta[e]pentalen-7-yl] ester (156a).

155a **156a**

DMAP (488.3 mg, 4.00 mmol) and phenyl chlorothionoformate (0.41 mL, 3.0 mmol) were added successively to a stirred solution of alcohol **155a** (154.2 mg, 0.652 mmol) in MeCN (7 mL). Stirring was continued for 24 h. The mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 10% EtOAc-hexane, gave thionocarbonate **156a** (204.3 mg, 84%) as a pure (^1H NMR, 200 MHz), white solid: FTIR (CH_2Cl_2 cast) 2953, 2867, 1738, 1591, 1490, 1465, 1457, 1408, 1384, 1366, 1244, 1199 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.93 (s, 3 H), 0.95 (s, 3 H), 0.99 (s, 3 H), 1.10 (s, 3 H), 1.29-1.53 (m, 4 H), 1.62-1.95 (m, 2 H), 2.23-2.55 (m, 2 H), 2.57 (ddd, *J* = 10.0, 10.0, 10.0 Hz, 1 H), 2.97 (dddd, *J* = 10.0, 10.0, 9.0, 7.0 Hz, 1 H), 5.59 (d, *J* = 7.0 Hz, 1 H), 7.06-7.16 (m, 2 H), 7.24-7.50 (m, 3 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 13.01 (q'), 19.73 (q'), 27.11 (q'), 29.21

(q'), 34.65 (t'), 35.15 (t'), 40.38 (t'), 42.32 (s'), 43.00 (t'), 46.69 (d'), 49.67 (s'), 53.49 (d'), 65.16 (s'), 90.12 (d'), 122.24 (d'), 126.92 (d'), 129.94 (d'), 153.74 (s'), 194.83 (s'), 220.67 (s'); exact mass *m/z* calcd for $C_{15}H_{23}O$ (M - $C_7H_5O_2S$) 219.17488, found 219.17448.

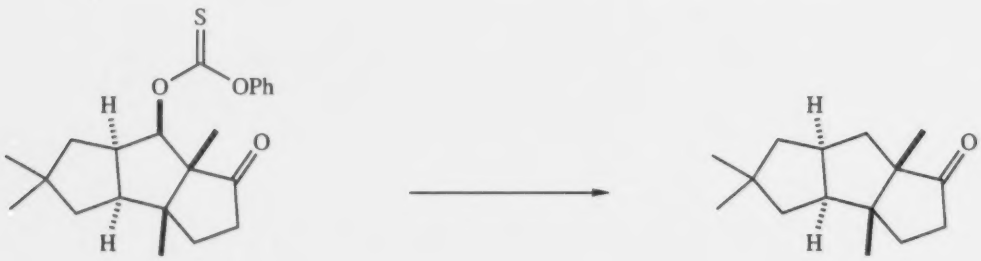
Thiocarbonic acid *O*-Phenyl *O*-[(3aα,3bβ,6aβ,7β,7aα)-(±)-decahydro-3a,5,5,7a-tetramethyl-1-oxo-(1*H*)-cyclopenta[e]pentalen-7-yl] ester (156b).

155b **156b**

DMAP (195.3 mg, 1.60 mmol) and phenyl chlorothionoformate (0.17 mL, 1.2 mmol) were added successively to a stirred solution of alcohol **155b** (56.7 mg, 0.240 mmol) in MeCN (3 mL). Stirring was continued for 24 h. The mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexane, gave thionocarbonate **156b** (66.3 mg, 74%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2952, 2864, 1741, 1591, 1490, 1466, 1456, 1406, 1384, 1366, 1292, 1280, 1220, 1200, cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 0.92 (s, 3 H), 0.94 (s,

3 H), 1.08 (s, 3 H), 1.11 (s, 3 H), 1.25-1.57 (m, 3 H), 1.67-2.27 (m, 5 H), 2.71-3.00 (m, 2 H), 5.12 (d, J = 1.5 Hz, 1 H), 7.01-7.13 (m, 2 H), 7.23-7.47 (m, 3 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 17.97 (q'), 18.58 (q'), 26.14 (q'), 29.03 (q'), 35.94 (t'), 37.24 (t'), 41.48 (s'), 44.42 (t'), 48.28 (t'), 51.25 (d'), 53.01 (s'), 55.50 (d'), 63.75 (s'), 100.92 (d'), 122.25 (d'), 126.87 (d'), 129.94 (d'), 153.63 (s'), 193.80 (s'), 218.59 (s'); exact mass *m/z* calcd for $C_{15}H_{23}O$ (M - $C_7H_5O_2S$) 219.17488, found 219.17451.

(3aα,3bβ,6aβ,7aα)-(±)-Decahydro-3a,5,5,7a-tetramethylcyclopenta[e]pentalen-1-one (157) from (156a).



156a **157**

Et_3B (1.0 M in pentane, 0.14 mL, 0.14 mmol) was added dropwise to a cooled (0 °C) and stirred solution of thionocarbonate **156a** (54.2 mg, 0.145 mmol) and Bu_3SnH (0.16 mL, 0.58 mmol) in hexane (3 mL). Air (20 mL) was injected into the flask and stirring was continued for 1 h, at which point reaction was still incomplete (TLC control, silica, 10% EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.0 x 10 cm),

using 5% EtOAc-hexane, gave mixed fractions of starting material and product. Fractions containing starting material and/or product were combined and evaporated. The residue was resubjected to the original reaction conditions and, after 1 h, all starting material had been consumed (TLC control, above system). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.0 x 20 cm), using 5% EtOAc-hexane, gave ketone **157** (23.2 mg, 72%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2948, 2865, 1737, 1466, 1451, 1382, 1366; ^{1}H NMR (200 MHz, CD_2Cl_2) δ 0.90 (s, 3 H), 0.95 (s, 3 H), 1.01 (s, 3 H), 1.06 (s, 3 H), 1.07-1.30 (m, 2 H), 1.41 (br d, J = 9.0 Hz, 2 H), 1.60-1.83 (m, 3 H), 1.98-2.73 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 18.05 (q'), 18.93 (q'), 26.93 (q'), 29.45 (q'), 34.81 (t'), 35.38 (t'), 42.14 (d'), 42.41 (s'), 43.58 (t'), 43.62 (t'), 49.82 (t'), 51.70 (s'), 56.18 (d'), 61.30 (s'), 223.23 (s'); exact mass m/z calcd for $C_{15}H_{24}O$ 220.18271, found 220.18280.

(3aα,3bβ,6aβ,7aα)-(±)-Decahydro-3a,5,5,7a-tetramethylcyclopenta[e]pentalen-1-one (157) from (156b).

156b **157**

Et_3B (1.0 M in pentane, 0.18 mL, 0.18 mmol) was added dropwise to a cooled (0 °C) and stirred solution of thionocarbonate **156b** (68.6 mg, 0.184 mmol) and Bu_3SnH (0.20 mL, 0.74 mmol) in hexane (4 mL). Air (20 mL) was injected into the flask and stirring was continued for 1 h, at which point reaction was incomplete (TLC control, silica, 10% EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.0 x 10 cm), using 5% EtOAc-hexane, gave mixed fractions of starting material and product. Fractions containing starting material and/or product were combined and evaporated. The residue was resubjected to the original reaction conditions and, after 1 h, all starting material had been consumed (TLC control, above system). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.0 x 20 cm), using 5% EtOAc-hexane, gave ketone **157** (29.8 mg, 73%) as a

pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to material obtained in the previous experiment.

(1α,3aβ,3bα,6aα,7aβ)-(±)-Decahydro-3a,5,5,7a-tetramethyl-(1*H*)-cyclopenta[e]pentalen-1-ol [(±)-ceratopicanol] (1).

157 **1**

$NaBH_4$ (29.1 mg, 0.768 mmol) was added to a cooled (-20 °C) and stirred solution of ketone **157** (56.4 mg, 0.256 mmol) in MeOH (10 mL). Stirring was continued for 20 min, and then the mixture was quenched with water, allowed to warm to room temperature, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave alcohol **1** (46.3 mg, 81%) as a pure (^{1}H NMR, 200 MHz), white solid: mp 67-68 °C. The ^{1}H NMR,[22] and ^{13}C NMR[21] spectra corresponded with the reported data. Exact mass calcd for $C_{15}H_{26}O$ 222.19836, found 222.19828.

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75. Phosphomolybdic acid (15 g) and cerric ammonium sulfate (2.5 g) dissolved in a mixture of water (985 mL) and concentrated sulfuric acid (15 mL).

CHAPTER II

Introduction - Peptide Synthesis

A. Polypeptide Biosynthesis[1]

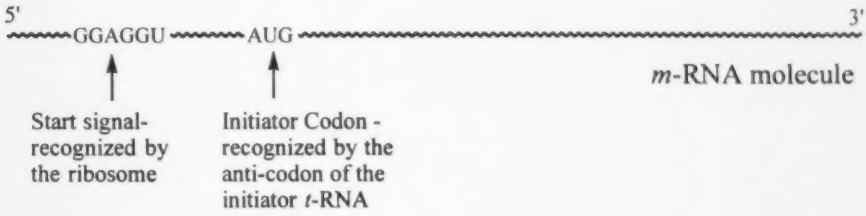
Most *in vivo* polypeptide synthesis occurs at ribosomes, which may be considered as molecular machines that coordinate the interaction of transfer-RNA (*t*-RNA), messenger-RNA (*m*-RNA), and proteins in the complex process of protein synthesis. A ribosome is made up of numerous proteins and a small number of RNA molecules, and is constructed in such a way as to provide *inter alia* binding sites that are needed for peptide chain growth. The two key binding sites are called the peptidyl site [(P)-site], and the aminoacyl site [(A)-site].

In biochemical terminology, protein synthesis is referred to as *translation* because the four-letter alphabet of nucleic acids is translated into an entirely different alphabet of proteins. *m*-RNA is the polynucleotide that codes for the synthesis of a specific protein, in other words, the base sequence of the *m*-RNA determines the amino acid sequence of the growing protein. Specific three-nucleotide sequences (called codons) on the *m*-RNA code for (i.e. are translated into) specific amino acids. These

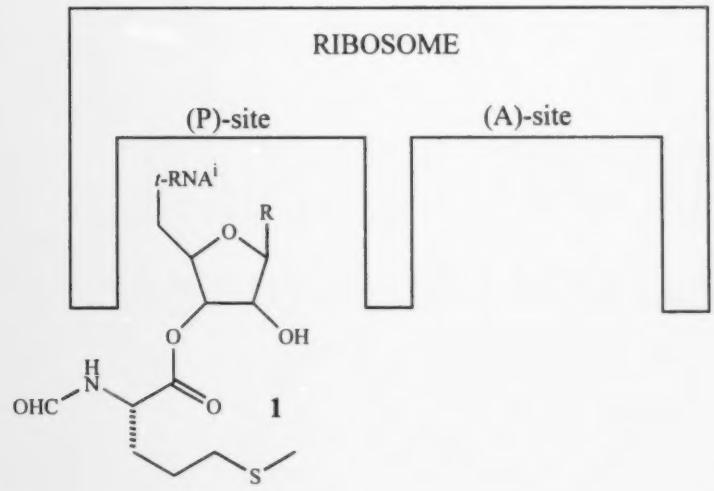
codons are identified at the ribosome by specific *t*-RNA's that bring the appropriate amino acids to the binding sites. The actual process of protein synthesis is viewed as taking place in three stages: initiation, elongation, and termination, and each of these is discussed in the following paragraphs.

INITIATION

Step 1:



Step 2:



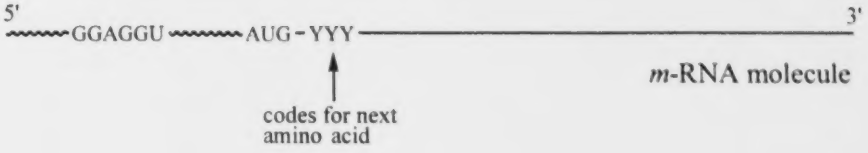
Scheme 1

Initiation (Scheme 1): The ribosomal RNA recognizes a purine-rich sequence—a sequence specific for that particular ribosome—near the 5' end of a *m*-RNA that is transiently associated with the ribosome, and the recognition event triggers protein synthesis. Next, the anti-codon of a initiator *t*-RNA recognizes a start codon on the *m*-RNA (step 1). For bacteria the initiator codon on the *m*-RNA is always either AUG or GUG. Docking of the initiator *t*-RNA (with the *m*-RNA) brings its specific amino acid to the (P)-site on the ribosome (step 2). The initiator *t*-RNA corresponding to the *m*-RNA codon AUG brings the amino acid formyl methionine to the (P)-site. In the formylmethionyl *t*-RNA molecule (**1**) the carboxyl end of formyl methionine is bonded to the 3' end of the *t*-RNA. The *t*-RNA portion fits into the (P)-site, thus ending the initiation stage.

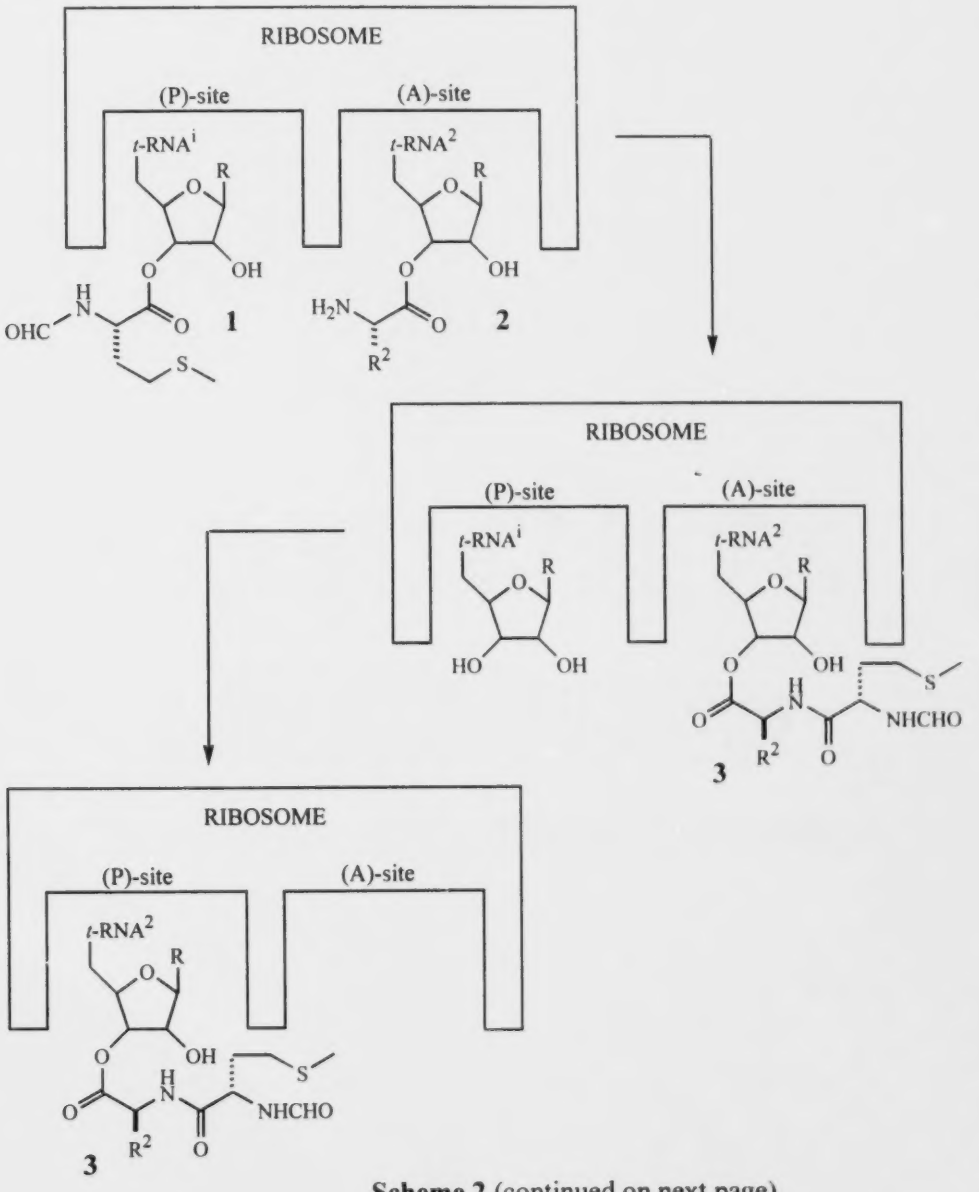
Elongation (Scheme 2): The next codon on the *m*-RNA is read by the anti-codon of its specific aminoacyl *t*-RNA (step 1 of Scheme 2) and this molecule (**2**) docks in the (A)-site on the ribosome. The amine group of the aminoacyl *t*-RNA at the (A)-site then attacks the carbonyl of the formylmethionyl *t*-RNA at the (P)-site (step 2), displacing the *t*-RNA portion of the initiator *t*-RNA. The newly formed

ELONGATION

Step 1:



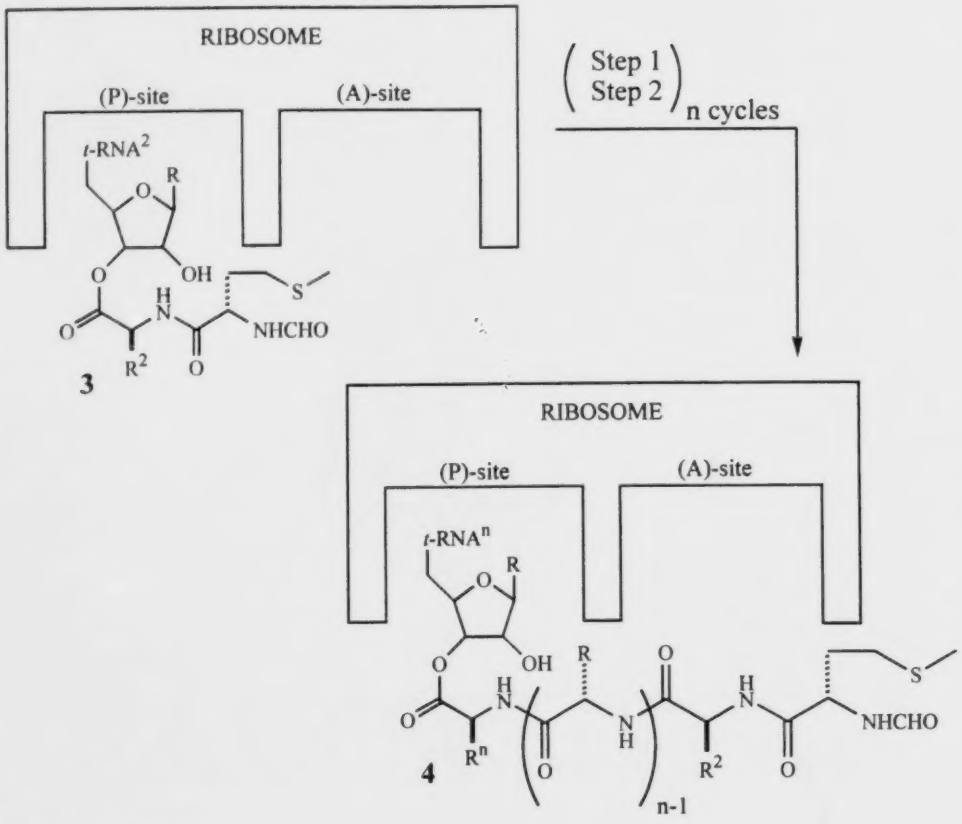
Step 2:



Scheme 2 (continued on next page)

ELONGATION (cont'd)

Step 3:



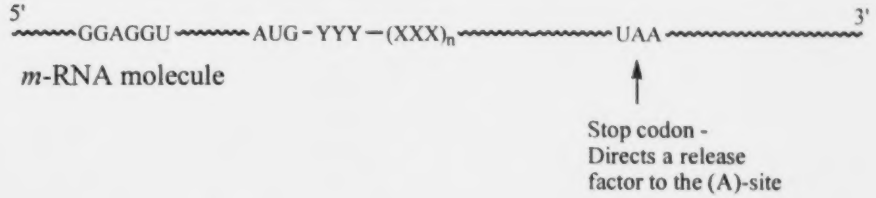
Scheme 2 (cont'd)

dipeptidyl *t*-RNA (**3**) is then moved from the (A)-site to the (P)-site, and the entire elongation cycle (steps 1 & 2 of Scheme 2) is repeated, the next codon being recognized by the anticodon of the appropriate aminoacyl *t*-RNA. This latter molecule then occupies the (A)-site. Amine attack at the dipeptidyl *t*-RNA carboxyl terminus again releases the *t*-RNA portion and generates a tripeptidyl *t*-RNA molecule.

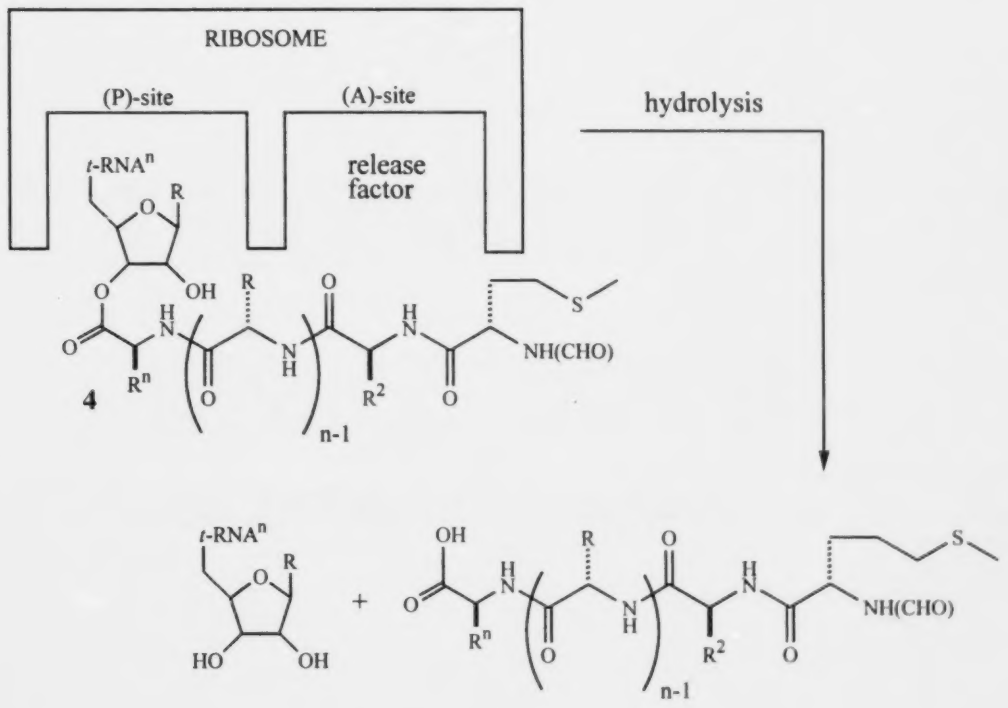
Finally, this molecule is itself transferred to the (P)-site. In this repetitive process the polypeptide continues to grow (step 3) from the carboxyl terminus, until the *m*-RNA codes for elongation to stop.

TERMINATION

Step 1:



Step 2:



Scheme 3

Termination (Scheme 3): Once the peptide has been elongated to its prescribed length (**4**), a stop codon on the *m*-RNA (UAA, UGA, or UAG) is recognized (step 1), and then no aminoacyl *t*-RNA is delivered to the (A)-site. Instead, a release factor from the ribosome binds to the (A)-site, and this event, in turn, activates an enzyme to hydrolyze the last acyl-*t*-RNA bond (step 2), freeing the carboxyl terminus of the peptide and allowing it to leave the ribosome.

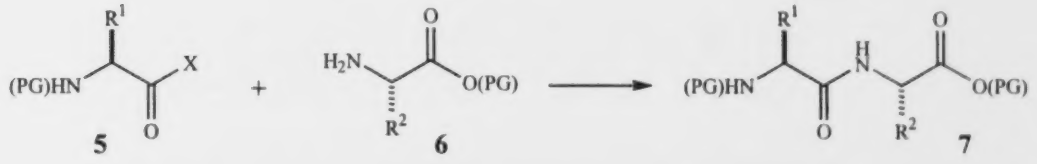
While the preceding text is a greatly simplified summary of *in vivo* peptide synthesis, it serves to emphasize three noteworthy observations:

1) As already mentioned, chain growth occurs at the carboxyl terminus.
2) The carbonyl that is attacked by the incoming amine group is connected, through an *ordinary ester linkage*, to the 3' end of a *t*-RNA molecule.
3) The carbonyl of aliphatic esters is relatively inactive, compared to the carbonyl of an acid chloride, for example, and so the success of the acyl transfer must rest, probably in large part, on the fact that operation of the ribosome brings the amine of the aminoacyl *t*-RNA molecule at the (A)-site into close proximity with the carbonyl at the (P)-site, thus enhancing the chance of nucleophilic attack.

The above considerations have all played a significant role in the development of new methods for polypeptide synthesis.

B. Development of Solution Peptide Synthesis, and Limitations of the Method

The first syntheses of simple peptide derivatives were reported by Curtius[2] and by Fischer[3] near the beginning of the 20th century. Since that time, significant effort has gone into the development of ways to synthesize polypeptides in solution. The classical methods for peptide synthesis are covered in detail by Miklos Bodansky in a number of excellent texts,[4] but an overview of the more important developments and the limitations of the methods will serve to explain the need for the research considered in the discussion section of this chapter.

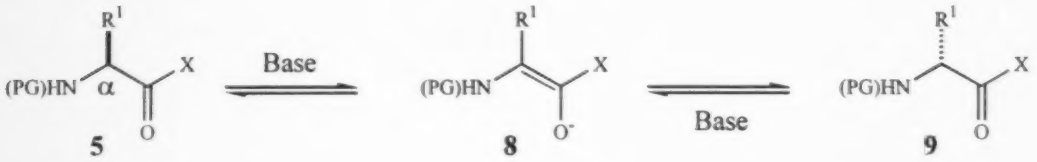


X = electron withdrawing group
(PG) = protecting group

Scheme 4

Formation of a dipeptide (**7**, Scheme 4) involves reaction of the amino terminus of a carboxyl-protected amino acid (**6**) with the carboxyl terminus of an *N*-protected amino

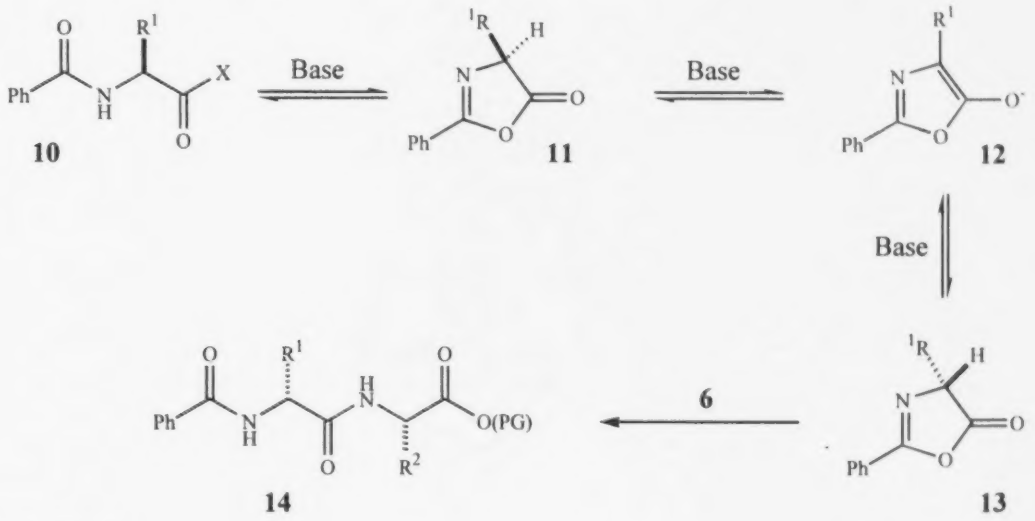
acid (**5**). The carboxyl terminus must be activated (i.e. X is an electron-withdrawing group). While *in vivo* peptide synthesis does not involve direct chemical activation of the carboxyl terminus, activation is necessary in solution peptide synthesis to permit intermolecular nucleophilic attack by the amine. The main problem with this activation is that the electron-withdrawing effect extends to the α-carbon atom, making the attached hydrogen more susceptible to abstraction (Scheme 5). The result of equilibration



Scheme 5

(**5**→**8**→**9**, Scheme 5) would, of course, be racemization[5] at the stereogenic carbon. While this simple proton abstraction mechanism is not a significant pathway, racemization of an activated amino acid derivative is a major problem in peptide synthesis. The dominant mechanism for racemization involves the intermediacy of azalactones (Scheme 6).[6] If the amino terminus is protected in the form of a benzamide (**10**)—a popular protection method in early synthetic efforts—then formation of azalactone **11** and subsequent

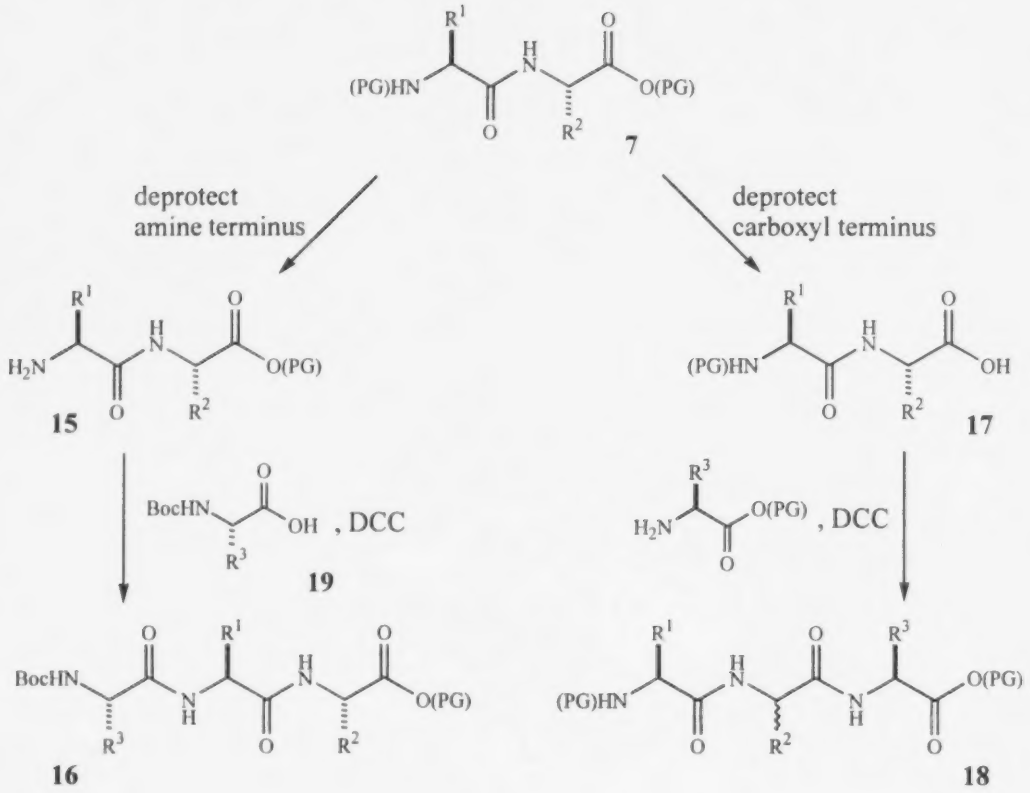
racemization (**11→12→13**) is extremely easy. Formation of dipeptide **14** from racemized azalactone **13** would give a diastereomer of the dipeptide **7** (Scheme 4), that was actually desired.



Scheme 6

In the early 1930's Bergman and Zervas reported use of the benzyloxycarbonyl (Cbz) group for amine protection.[7] The use of this and other urethane-type protecting groups[4] was found to suppress azalactone formation and therefore racemization as well.

Besides studies aimed at developing better forms of amine protection, efforts were also made to create milder carbonyl activating groups and, with the discovery of dicyclohexylcarbodiimide (DCC) as a coupling reagent,[8] the problem of synthesizing dipeptides of high optical purity was solved.



Scheme 7

In order to convert dipeptide **7** into a tripeptide, two possibilities exist (Scheme 7): Deprotection of the carboxyl terminus (**7**→**17**) and addition of the next amino acid to this end (**17**→**18**), or deprotection of the amino terminus (**7**→**15**) and linkage of this terminus to the next amino acid (**15**→**16**). The problem with the former possibility (**7**→**17**→**18**) is that activation of the newly deprotected carboxyl group of **17** would lead to racemization at the carbon α to the activated carbonyl (since the *N*-acyl

unit is not of the urethane type), giving **18** as a mixture of diastereomers. Therefore it is necessary to use the alternative approach of deprotecting the amine (**7**→**15**), and linking it with another carbonyl-activated amino acid having its own amino terminus protected as a urethane (**19**). In this way, chain growth occurs at the amino terminus, not the carboxyl terminus as is the case for *in vivo* peptide synthesis.

The methods of solution chemistry work well for the preparation of small polypeptides, but the limitations of these methods become apparent when synthesis of longer chains (longer than about five amino acid units) are attempted. In many cases, protection of the side chains of the amino acid residues is necessary to preclude side reactions.[4] With long peptide chains and, therefore, more protecting groups, the solubility of the masked peptides becomes increasingly limited. The result of decreased solubility is the need for higher dilutions and, consequently, longer reaction times. These, in turn, lead to a higher chance of side reactions,[4] including racemization. It is also more difficult to drive reactions to completion, and separation of the product from by-products and unreacted starting materials is laborious, and sometimes impossible. In practical terms, peptide synthesis in solution can usually only be used to make polypeptides of only about ten amino acid residues or less. In order to

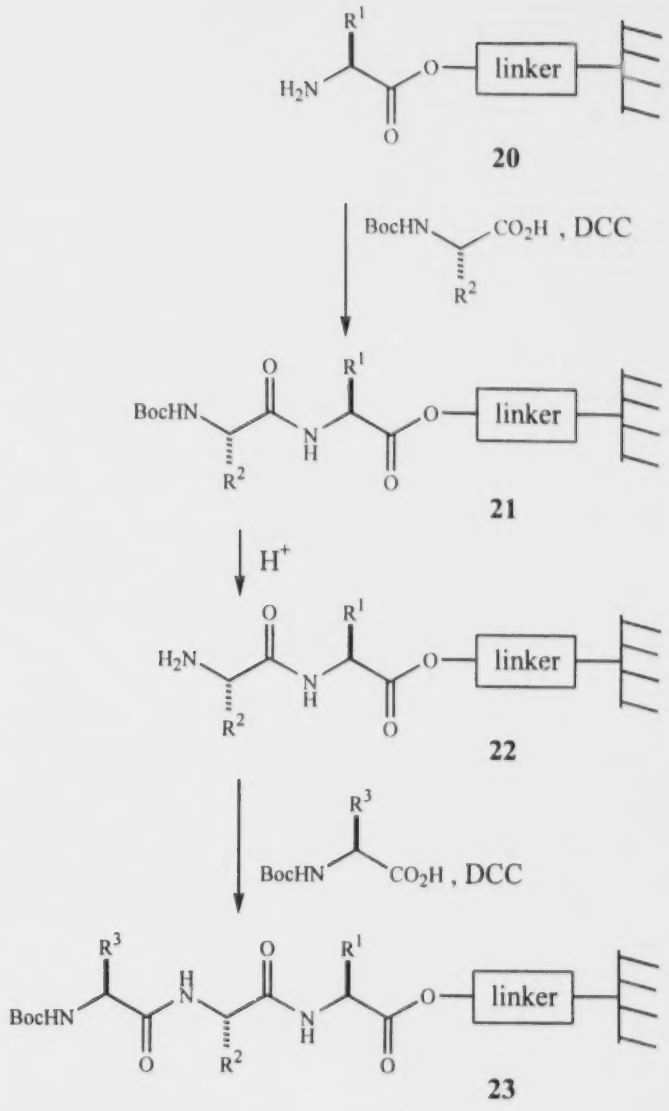
make longer chains of high purity the technique of solid phase peptide synthesis is almost always employed.

C. Development of Solid Phase Peptide Synthesis, and Limitations of the Method

In the early 1960's Merrifield introduced the technique of solid phase peptide synthesis.[9,10] This method revolutionized the discipline of peptide synthesis, since it addressed the problem of low peptide solubility and dispensed with much of the need for complicated separation of reaction components.

In solid phase peptide synthesis, the carboxyl terminus of an amino acid is connected, through a linker, to an insoluble polymeric support (**20**). The various types of linkers and resins are discussed elsewhere,[4,10] but typically the resin is a suspension polymer of styrene with 1% of divinyl benzene. Chloromethylation of the phenyl groups provides the points of attachment for connection of the linker. The bond between the linker and the carboxyl terminus of the first amino acid must be stable to manipulations involved in chain elongation, but must be cleavable, after chain elongation, by a method that will not damage the polypeptide.

A typical reaction cycle used in chain elongation (Scheme 8) begins by reacting the amino terminus of the polymer-bound amino acid with the carboxyl end of a suitably protected amino acid (**20**→**21**). The amino terminus of the



Scheme 8

newly formed dipeptide is deprotected (**21**→**22**) and then reacted with another amino acid (**22**→**23**). The elegance of the technique is that the reagents are simply poured through the polymer and, once complete reaction is accomplished, any

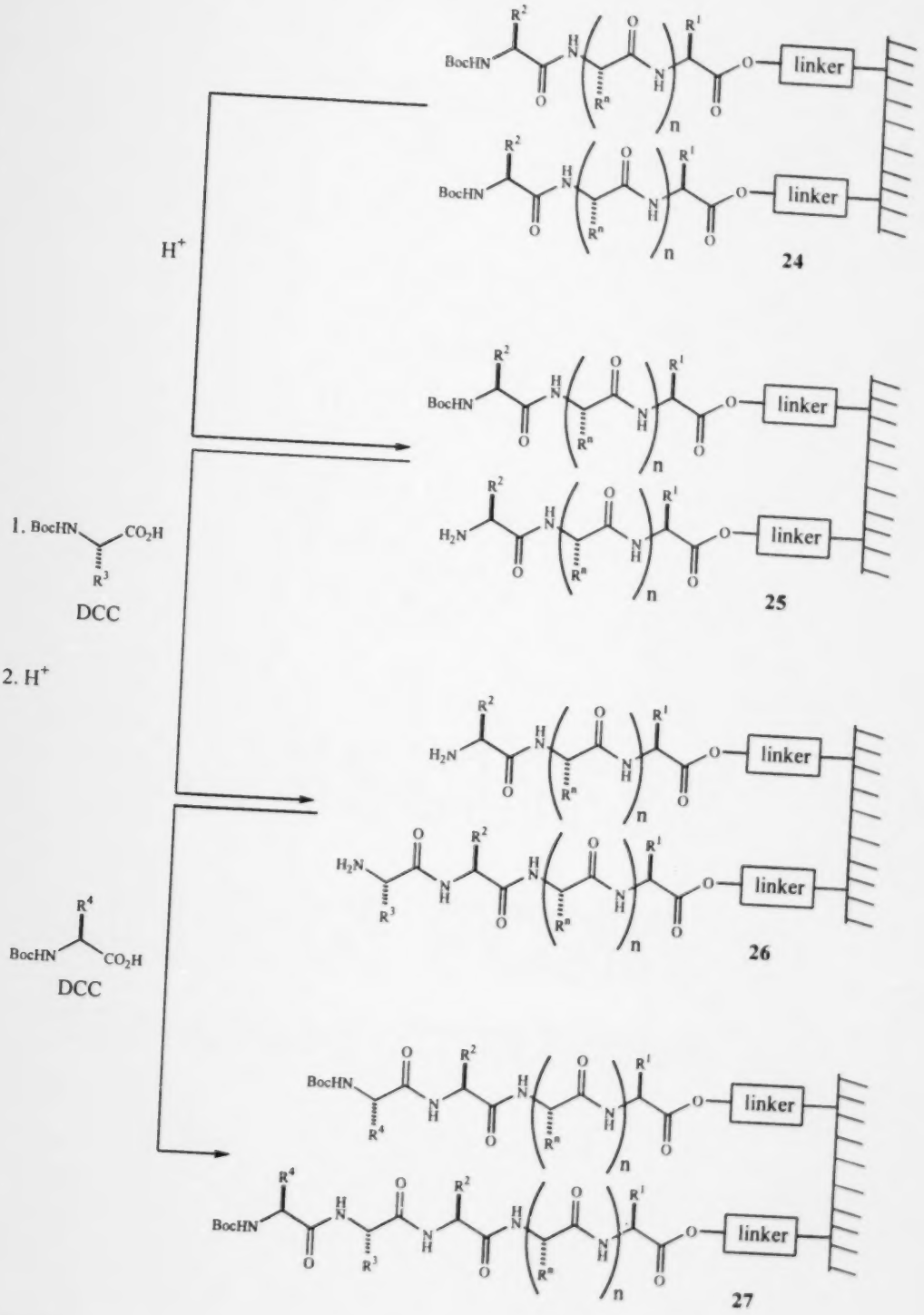
by-products or excess reagents are simply washed away with solvent.

A proper choice of protecting groups is the key to efficient synthesis. The blocking groups that are used on the side chains must be robust enough to survive deprotection of the amino terminus during chain elongation, but must also be removable once chain synthesis is complete. There are two blocking schemes that are commonly used. One scheme employs the acid sensitive Boc (*t*-butyloxycarbonyl) group to temporarily protect the amino termini. Boc protection is used in conjunction with side-chain blocking groups that are cleaved only under strongly acid conditions.

The other common protection scheme involves use of the Fmoc (9-fluorenylmethoxycarbonyl) group for amino protection. This group is removable under mildly basic conditions and, therefore, acid-sensitive protecting groups are used for the side chains.

In both approaches, once chain elongation is complete, the side chain protecting groups are removed (preferably in one step), and the carboxyl terminus is liberated from the linker.

Solid phase peptide synthesis provides an extremely efficient way to construct peptide chains of lengths approaching 100 residues. Beyond this length, however, problems of deletion sequences (Scheme 9) become significant. A deletion sequence results when one of the reactions in the elongation cycle does not go to completion.

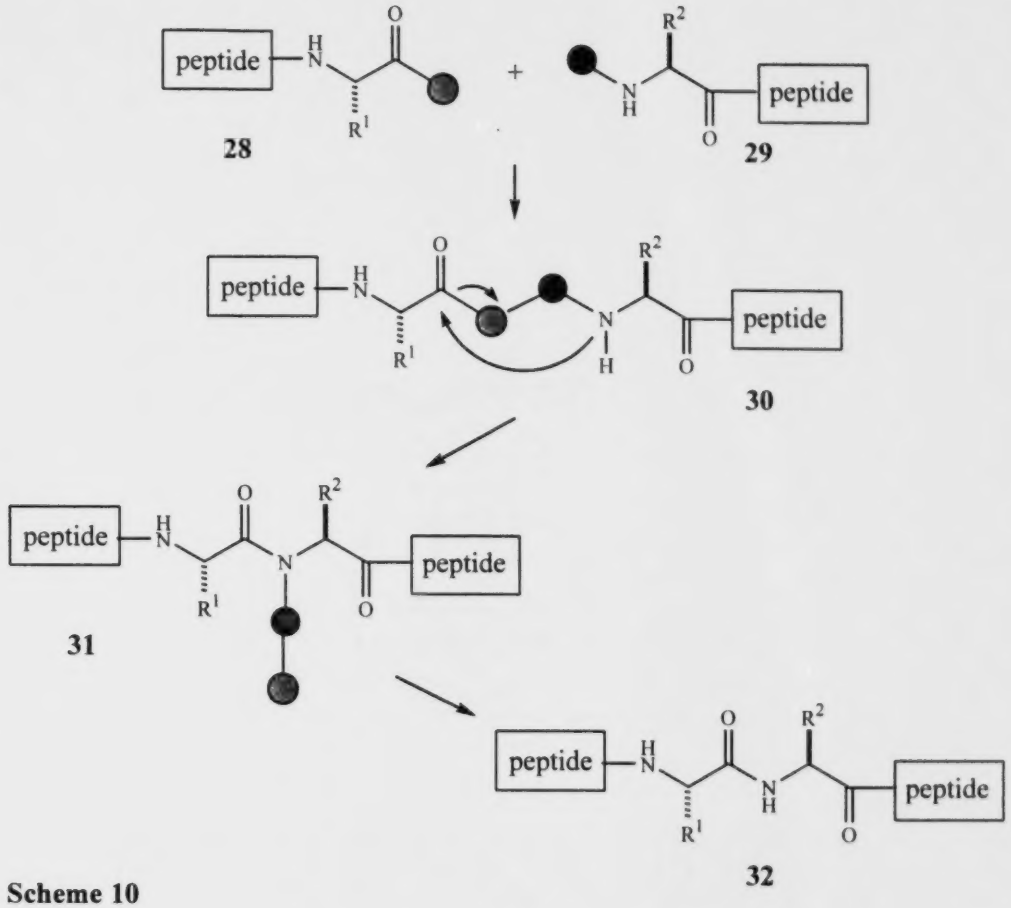


Scheme 9

For example, if the protecting group at the amino terminus is not removed from one of the chains (**24→25**), then that chain will not be lengthened in the next step. The protecting group may be removed in the following cycle though, and in this way the chain will be built up missing one of the residues (**25→26→27**). Separation of this shorter chain would prove extremely difficult, and the purity of the peptide would be compromised. Normally, deletion sequences are not a major problem for short sequences, because use of large excesses of reagents ensures complete reaction. But for long peptide chains, with many side chain protecting groups, access to the amino terminus becomes hindered, and achieving complete reaction is difficult. Because of this limitation, the search for efficient methods of making peptide chains of over 100 residues is an active field of research.

D. Peptide Segment Coupling By Intramolecular Condensation

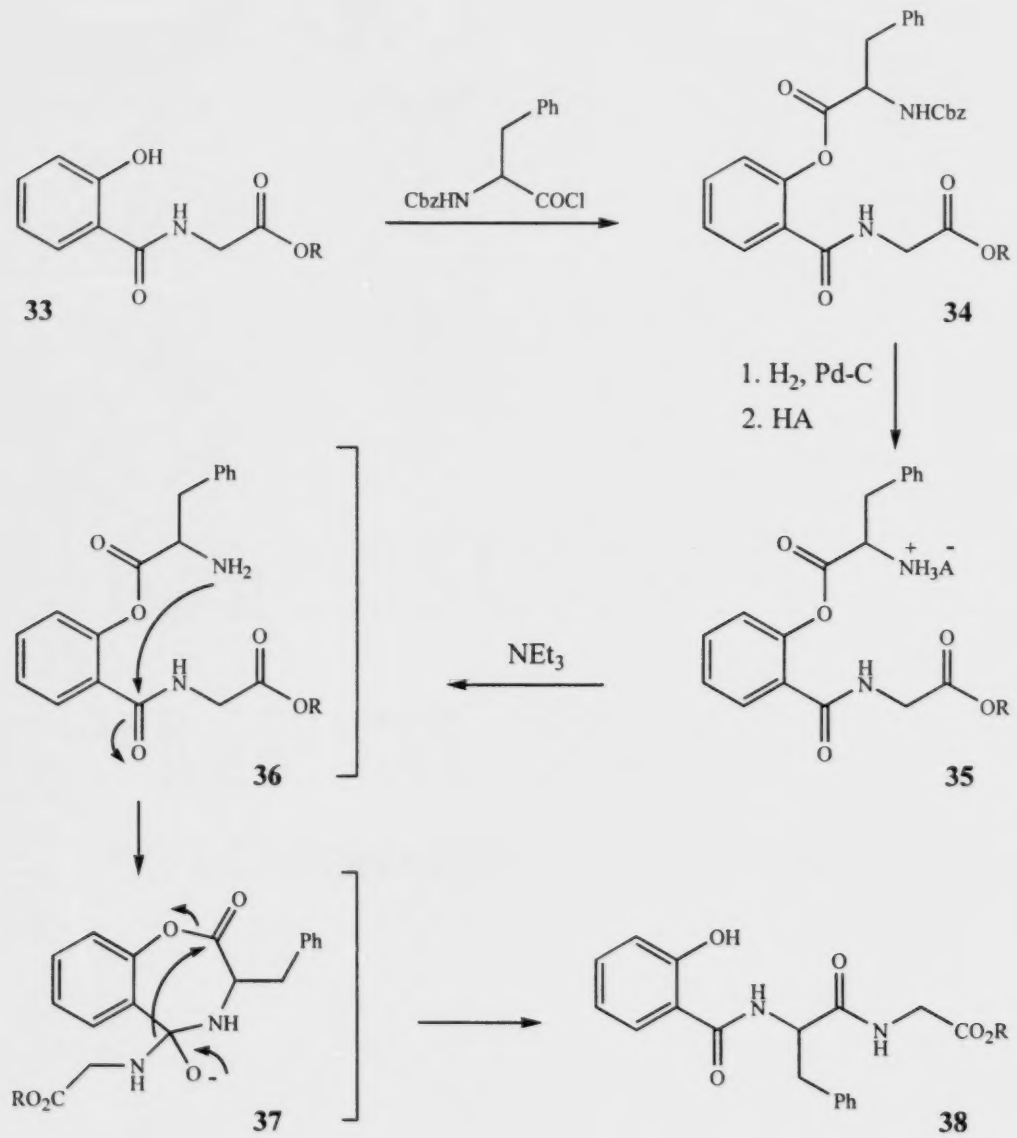
One concept for making long peptide chains that has started to receive considerable attention involves intramolecular peptide bond formation in solution. The general idea consists of bringing the amino terminus of one peptide segment in close proximity to the carboxyl terminus of another. In the conceptual example of Scheme 10, the carboxyl terminus of one peptide chain and the amino terminus of another peptide chain are manipulated such that



Scheme 10

they may be linked together, forming a single molecule (**28+29→30**). Intramolecular peptide bond formation can then occur (**30→31**), and the auxiliary can be cleaved (**31→32**). The advantages realized by using an intramolecular acyl transfer instead of the standard intermolecular peptide bond formation are significant. Firstly, the normal consequences of low solubility of long peptide chains is irrelevant because the intramolecular reaction is first order. Furthermore, the entropic advantage of having a high local

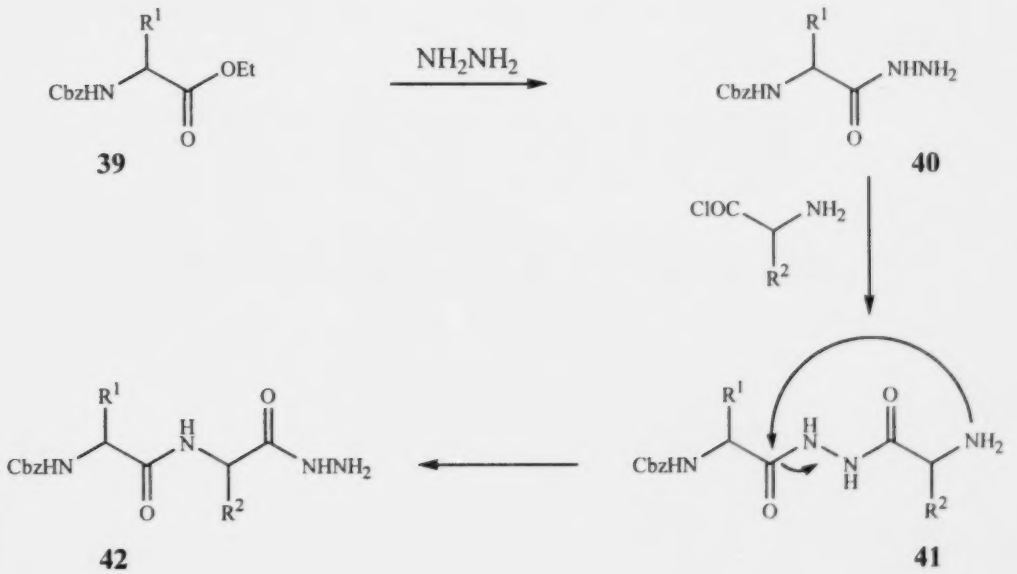
concentration of the amine and carbonyl can replace the enthalpic advantage of an activated carbonyl. In this way, peptide bond formation more closely mimics the *in vivo* process, since proximity effects, not activation, are used



Scheme 11

to promote nucleophilic attack by nitrogen on the acyl group.

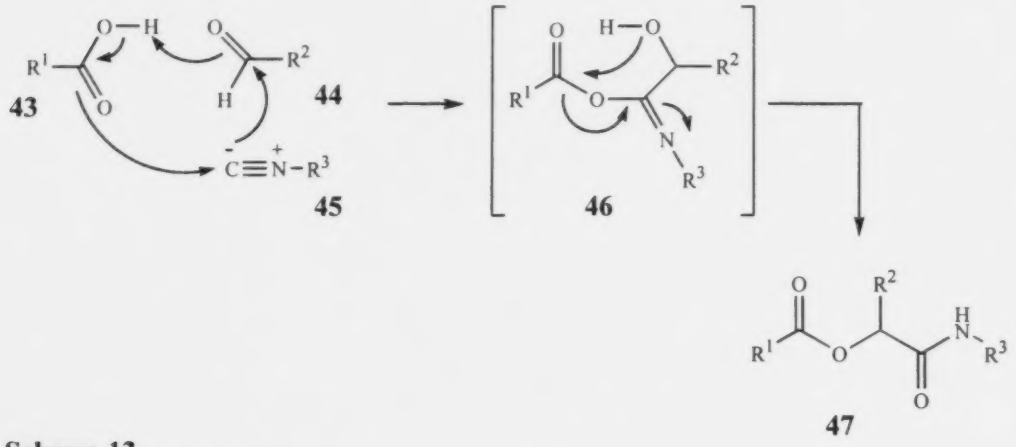
Although practical methods exploiting intramolecular *O→N* acyl transfer[11] have only appeared quite recently, the concept was first used by Brenner in the 1950's.[12] In his method (Scheme 11), phenol **33** was converted to phenylalanine derivative **34**. Deprotection and acidification gave salt **35**, which, upon treatment with base, rearranged (through **36** and **37**) affording dipeptide derivative **38**. Later,[13] Brenner studied synthesis (**39→40→41**) and rearrangement (**41→42**) of hydrazide **39** (Scheme 12). Here, peptide bond formation occurred through a six-membered ring. Neither of Brenner's methods was used to go beyond making a tripeptide, but they



Scheme 12

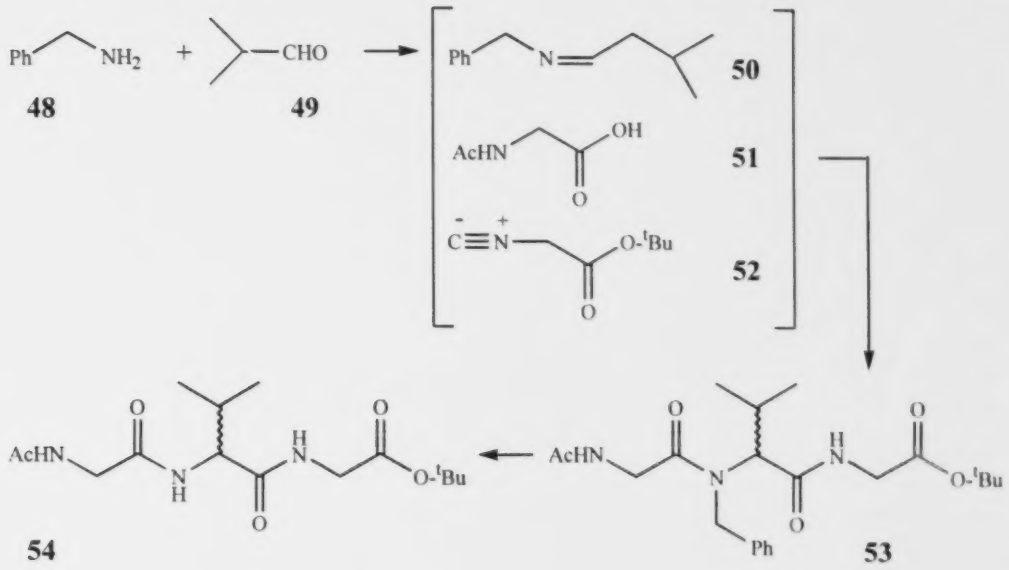
laid a foundation upon which current research is based.

Another early and imaginative use of intramolecular peptide bond formation was described by Ugi,[14] and makes use of the Passerini reaction.[15] In this process (Scheme 13),



Scheme 13

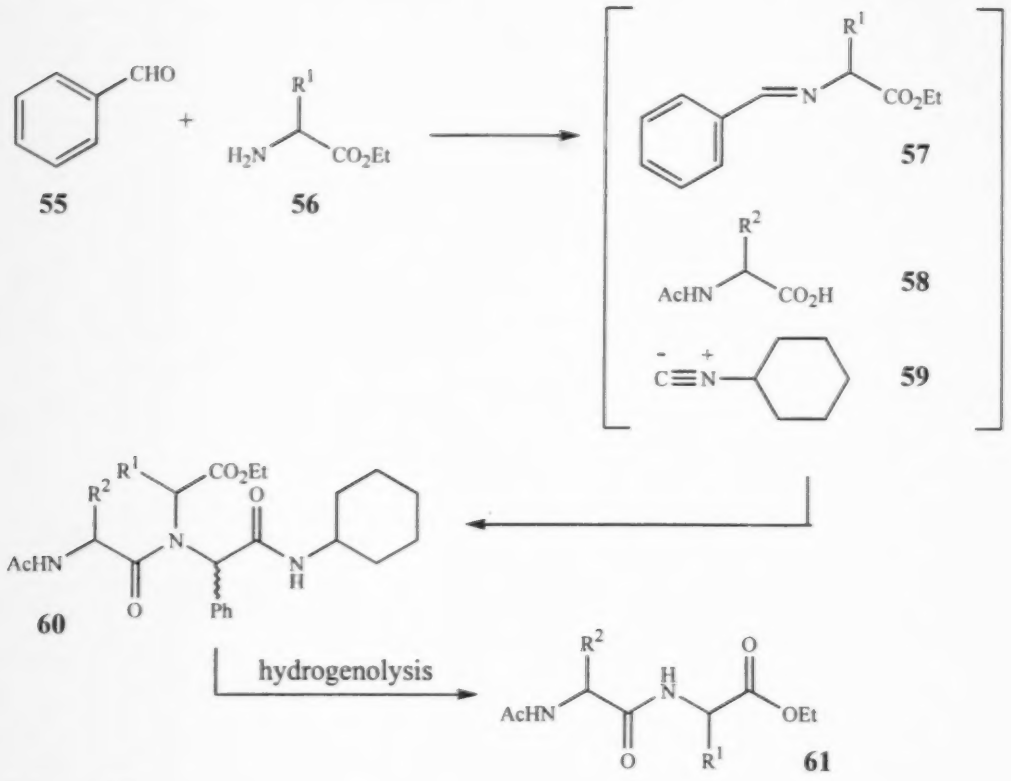
condensation of a carboxylic acid (**43**), an aldehyde (**44**), and an isonitrile (**45**) results in formation of intermediate **46**, which undergoes intramolecular acyl exchange to the α-(acyloxy)amide (**47**). Ugi recognized that the aldehyde should be replaceable by an imine. To test this idea, benzylamine (**48**) was condensed with isobutyraldehyde (**49**) to give imine **50** (Scheme 14). When this imine was reacted with acetyl glycine (**51**) and *t*-butyl isocyanoacetate (**52**), two peptide bonds were formed, furnishing tripeptide derivative **53**. Debenzylation would then give the terminal-protected



Scheme 14

tripeptide **54**, but this step does not appear to have been tried in this particular example. This method results in creation of a stereogenic centre on the peptide backbone where the valine side chain is located. Compound **53**, of course, is a racemate, but Ugi has noted[16] that use of optically pure α-phenylethylamine in place of benzylamine results in good diastereoselectivity in the four-component condensation. Isolation of the major diastereomer would still be necessary, however.

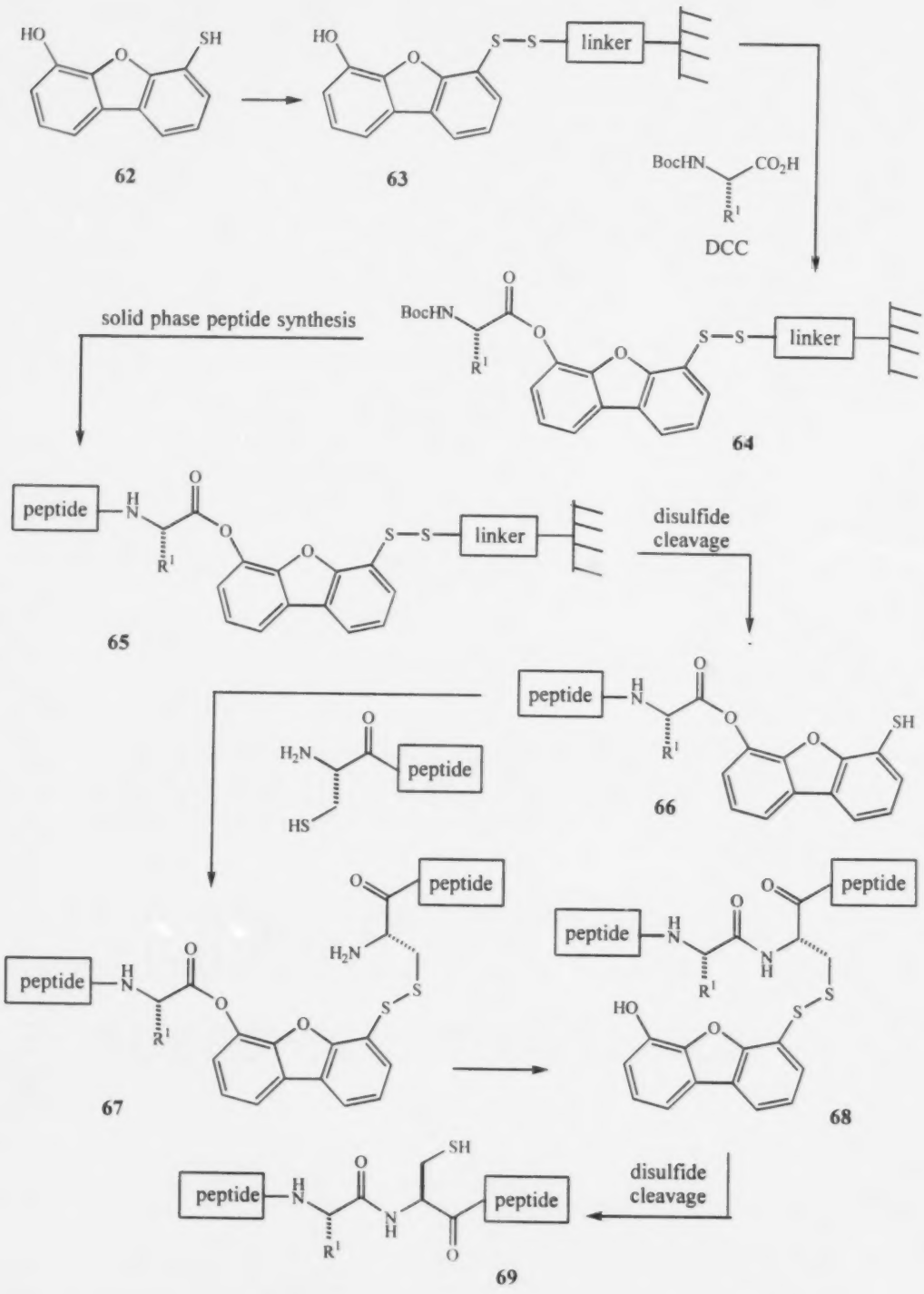
Meienhofer recognized a more practical application[17] of the Ugi reaction. Rather then try to form two peptide bonds at once and create a new stereogenic centre, Meienhofer was content with formation of just one peptide bond (Scheme 15).



Scheme 15

Carboxyl protected amino acid **56** can be condensed with benzaldehyde (**55**) to give imine **57**. When this imine was reacted with *N*-protected amino acid **58** and isonitrile **59**, condensation product **60** was formed. Cleavage of the *N*-benzyl bond furnishes the protected dipeptide **61**. The advantage of this method over Ugi's is that it does not involve creation of a new stereogenic centre and the associated problem of diastereoselectivity. Like the methods of Brenner and Ugi, Meienhofer's approach has been tested only for short peptide chains.

With the preceding examples offering inspiration, three groups have recently published results where long peptide chains were made by intramolecular peptide bond formation. The Kemp group has made a long and detailed study using various aromatic ring systems as templates through which the reacting amine and carboxyl termini are brought into close proximity.[18] The results were only moderately successful when intramolecular *O*→*N* acyl transfer proceeded through 5- or 6-membered rings,[19] but good results were realized when transfer was via 9- and 12-membered rings.[18a,c] The template that has been studied extensively is dibenzofuran **62** (Scheme 16). This compound was bound, through a disulfide link, to a polymeric support (**62**→**63**)[18b] and then the phenol moiety was acylated with an amino acid (**63**→**64**). Solid phase peptide synthesis[10,18b] was then used to construct a peptide chain. When this chain was built to the desired length (**64**→**65**), the disulfide bond linking the aromatic template to the resin was cleaved (**65**→**66**). A new disulfide bond was then formed[18f,18h] between the template and an *N*-terminal cysteine residue of another peptide chain (**66**→**67**). A feature of the substitution pattern on the rigid aryl template is that the amino terminus of the second peptide chain is in close proximity to the carboxyl terminus of the initial peptide chain. Peptide bond formation (**67**→**68**) then ensues via a 12-membered cyclic intermediate. At this point

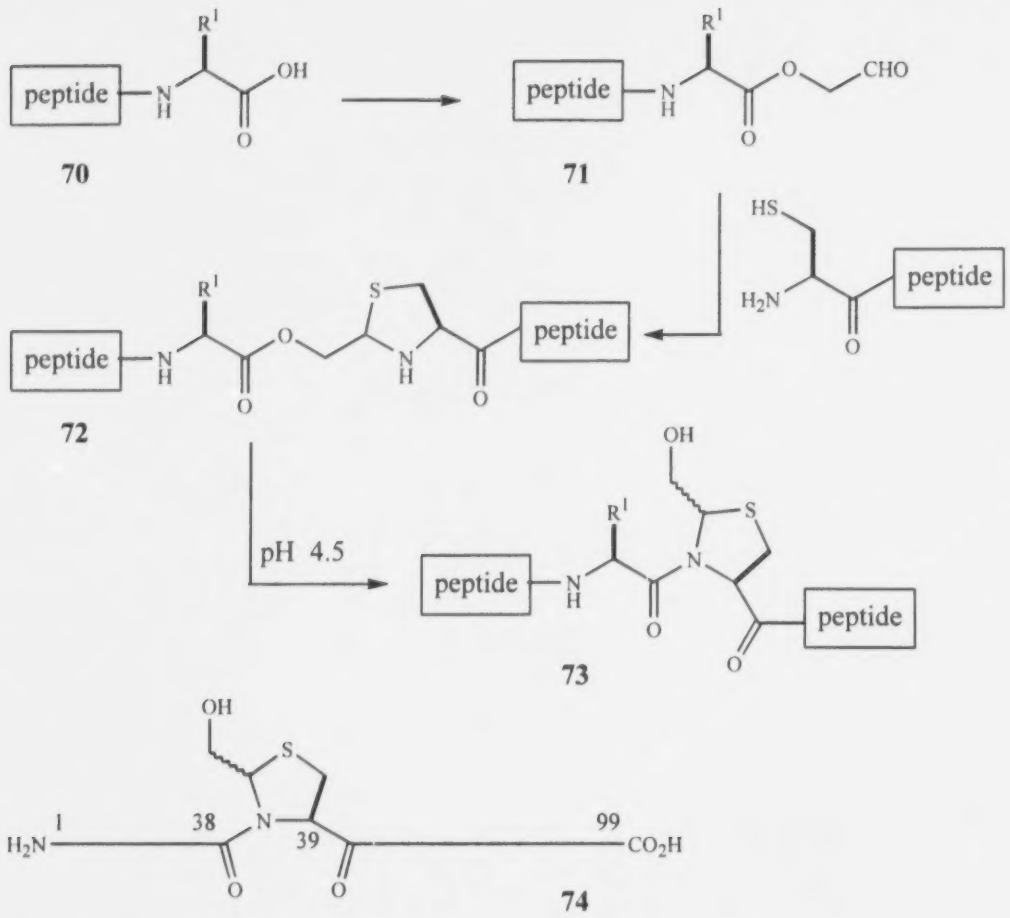

HO
SH
62
HO
S—S
linker
63
BocHN
CO2H
R1
DCC
solid phase peptide synthesis
BocHN
O
O
S—S
linker
64
peptide
H
N
O
R1
O
S—S
linker
65
disulfide
cleavage
peptide
H
N
O
R1
O
SH
66
H2N
O
peptide
HS
peptide
H2N
O
S
S
peptide
H
N
O
R1
O
67
peptide
H
N
O
R1
O
HO
S
S
peptide
68
peptide
H
N
O
R1
N
H
O
SH
peptide
H
N
O
R1
N
H
O
peptide
69
disulfide
cleavage

Scheme 16

the disulfide bond is cleaved, giving polypeptide **69**. Kemp has recently used this method to construct a peptide chain that contained 39 amino acid residues.[18i,j]

There are two very important properties of Kemp's method. Firstly, despite being mildly activated as a aromatic ester, there was no racemization at the carbon α to the carbonyl during acyl transfer.[18e] Secondly, formation of the disulfide link between the cysteine residue and the template (**66**→**67**) is a highly selective reaction. It was found that no protection of the side chains (except for other cysteine residues) was necessary[18d,i] and, since extensive protection often renders peptides insoluble, such problems were avoided during this intermolecular reaction. Furthermore, it was found that intramolecular peptide bond formation proceeded faster when the side chains were not protected,[18j] thus allowing less time for competing side reactions.[4]

Another innovative method for coupling peptide segments in solution has been reported by Tam.[20] In his procedure (Scheme 17), the carboxyl terminus of a polypeptide is converted to an *O*-glycoaldehyde (**70**→**71**). It should be noted that while the chemical methods shown for **70**→**71** were used to accomplish this transformation in model studies,[20a] Tam used either chemical or enzymatic methods[20b,c] for preparing the glycoaldehyde when working with long peptide chains.



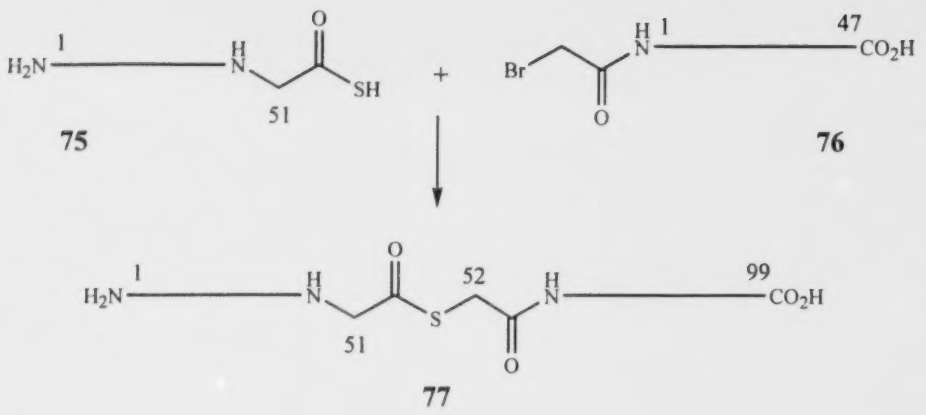
Scheme 17

With the glycoaldehyde moiety in place, treatment with an *N*-terminal cysteine residue of another polypeptide resulted in formation of a thiazolidine (**71→72**). This reaction between an alkyl aldehyde and a weak base is highly specific, since stronger bases such as side chain amino and guanidino groups did not require protection. Even if such side chain amino groups did react with the aldehyde, the process was reversible. *O→N* Acyl transfer then proceeded through a 5-

membered cyclic intermediate (**72**→**73**) after adjustment to slightly acidic pH. In this case, the transfer involves a secondary amine, and is significantly slower then the primary amine transfer in Kemp's method (Scheme 16, **67**→**68**). Nonetheless, racemization and side-reactions were not observed.

One feature of Tam's method is, of course, the presence of the thiazolidine unit. While it would be desirable to release the native cysteine residue by cleaving the glyceryl moiety, Tam has noted that the ring may be considered as a proline analog. He predicted that the presence of the (hydroxymethyl)thioproline analog would not change the backbone conformation of a proline-containing peptide. Indeed, synthesis of a 99-residue HIV-1 protease analog (**74**) containing a (hydroxymethyl)thioproline residue at position 39 was completed by Tam,[20c] and this analog retained full activity when compared to the native enzyme.

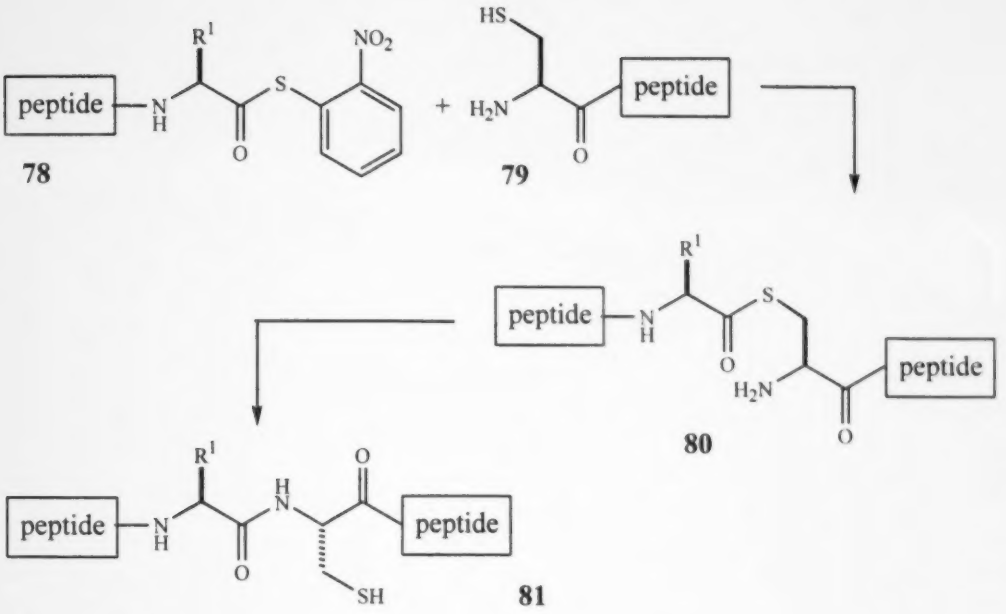
Another synthesis of an HIV-1 protease analog has been reported by Kent.[21] In his method (Scheme 18), a 51-residue polypeptide with an α-thiocarboxyl-containing glycine residue at the carboxyl terminus (**75**), and a 47-residue polypeptide that was protected with a bromoacetyl group at the amino terminus (**76**) were made, using solid phase peptide synthesis. When these polypeptides were reacted in solution adjusted to pH 4.3, intermolecular substitution proceeded to give protease analog **77**, which had a thioester linkage



Scheme 18

(rather than a peptide bond) between residue 51 and 52. In this case intramolecular peptide bond formation does not occur. Here the bromoacetyl "protecting group" is an isosteric replacement for the glycine residue at position 52. In addition, because of the high selectivity of the nucleophilic displacement, absolutely no protecting groups were needed on either peptide segment. Consequently, solubility of the fragments was high, and the concentration-dependent substitution reaction proceeded quickly. Like Tam's analog (**74**), Kent's analog (**77**) showed the same specific activity as the native enzyme.

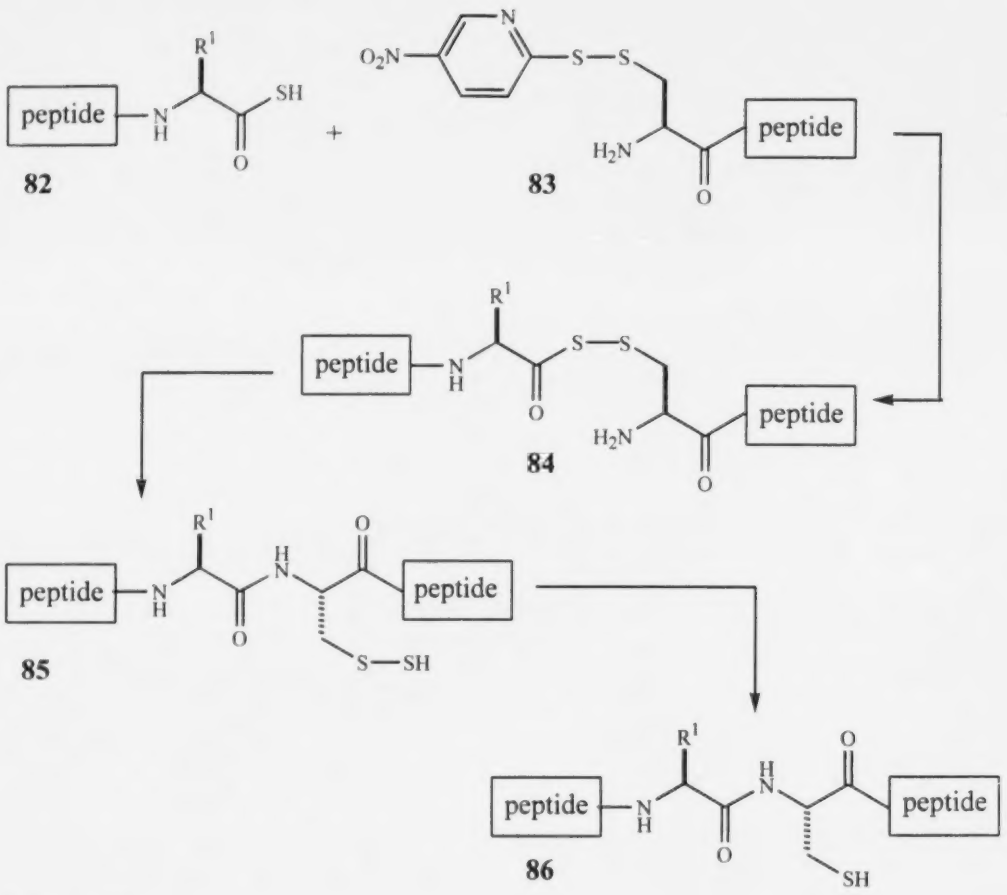
Kent has also developed a method that couples peptide segments via intramolecular acyl transfer.[22] In this case (Scheme 19), one peptide segment (**78**) had a thioester linkage at the carboxyl terminus, while the other peptide segment (**79**) required a cysteine residue at the amino terminus. Nucleophilic attack by the cysteine residue at



Scheme 19

the thioester gave intermediate **80**, and this rapidly underwent intramolecular acyl transfer, to furnish polypeptide **81**. With this technique a natural polypeptide is formed with no sign of racemization and, once again, protection of the side chains is not necessary. Kent has used this method to prepare the 72-residue polypeptide human *interleukin 8*. It should be noted that the linkage between the two segments must be at the site of a cysteine residue, and it is not yet clear to what extent—if any—the *mild* activation inherent in the structure of **78** could be detrimental.

Recently, Tam has introduced another variation of the preceding methods.[23] In this case (Scheme 20) the carboxyl



Scheme 20

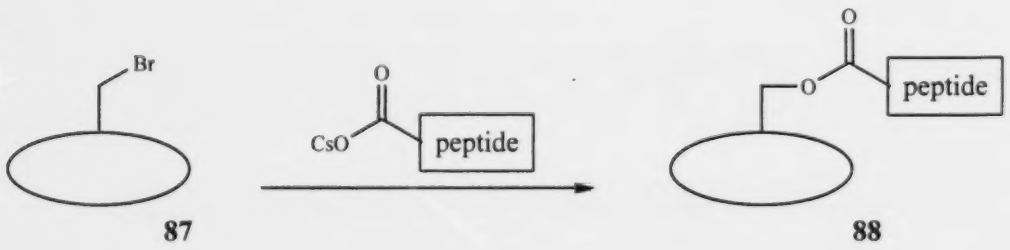
terminus of one peptide chain (**82**) must be a thiocarboxylic acid and the other segment (**83**) requires an *N*-terminal cysteine residue that is present as an aryl disulfide. This activated thiol side chain is captured by **82**, forming acyl disulfide **84**. Rapid *S*→*N* acyl transfer through a 6-membered cyclic intermediate then occurs, to give hydrodisulfide **85**. Thiolytic reduction releases the native cysteine and completes the synthesis of polypeptide **86**.

The methods of Kemp, Tam, and Kent are truly powerful techniques for the synthesis of long polypeptides. With the exception of the process discussed in Scheme 18 though, all of the procedures require the presence of a cysteine residue at the *N*-terminus of one of the fragments. In Scheme 18 a glycine residue was required. There is a definite need for more general methods that do not require the presence of a specific residue, and research in this direction will undoubtedly lead to novel ways of synthesizing polypeptides.

Results and Discussion:

Our aim was to examine intramolecular *O→N* acyl transfer, and we had in mind a number of different systems that might undergo this process in a way that would be compatible with applications in the field of peptide synthesis. Each of these model systems had to have a number of common features that are required to accomplish the task at hand:

1) The templates must contain a primary (or secondary) bromine group to allow attachment of the carboxyl terminus of a peptide chain (Scheme 21). If the carboxyl terminus is converted into its corresponding cesium salt, and then reacted with a bromide, displacement of bromide ion (**87→88**) proceeds quickly, at room temperature.

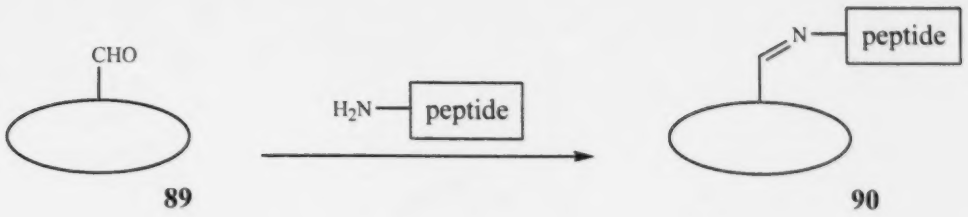


87 **88**

Scheme 21

2) The templates also required an aldehyde so that the amino terminus of a peptide chain could be joined (Scheme 22). Primary amines condense with aldehydes,[24] also at room

temperature, in the presence of molecular sieves, to form imines (**89→90**).

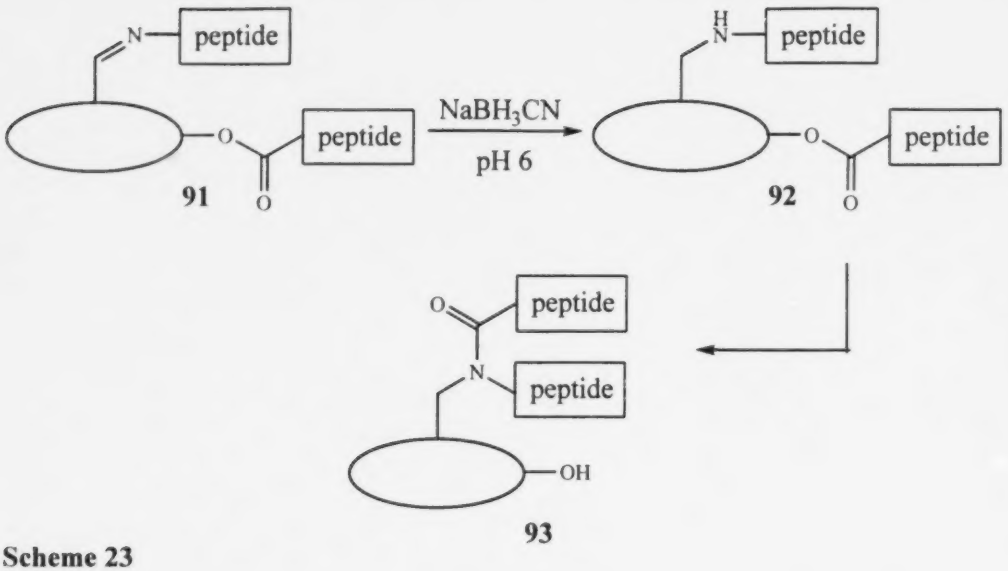


89 **90**

Scheme 22

As mentioned in the introduction it is desirable to use as few protecting groups as possible on the side chains, during coupling of peptide segments. Both of the reactions just mentioned are highly specific, with only lysine and arginine side chains needing protection during condensation of the amino terminus with the aldehyde (**89→90**), and only aspartic and glutamic acid side chains needing protection during bromide displacement by the carboxyl terminus (**87→88**).

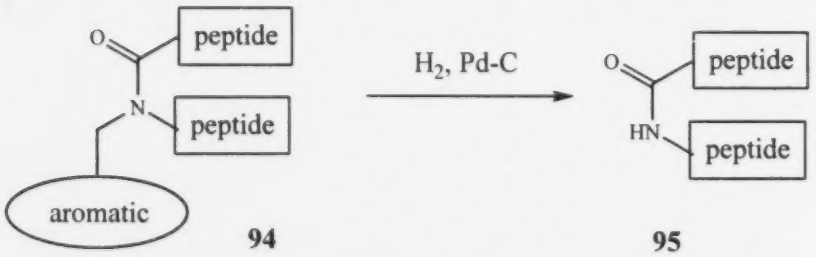
3) The third common feature of the systems we planned to consider involves the use of $NaBH_3CN$, under pH controlled conditions[25] (Scheme 23), to reduce the imine to an amine (**91→92**). If the imine and carbonyl group are in close proximity (see below) then, after the necessary imine-reduction, *O→N* acyl transfer (**92→93**) could proceed.



Scheme 23

4) The final aspect of our approach was to use an *aromatic* aldehyde, as a handle to link the amino terminus of one peptide chain (Scheme 24). The reason for using the aromatic group is, of course, that once peptide bond formation has been completed, the peptide chain can be cleaved from the template by hydrogenolysis (**94→95**).

Before discussing the syntheses that we performed,



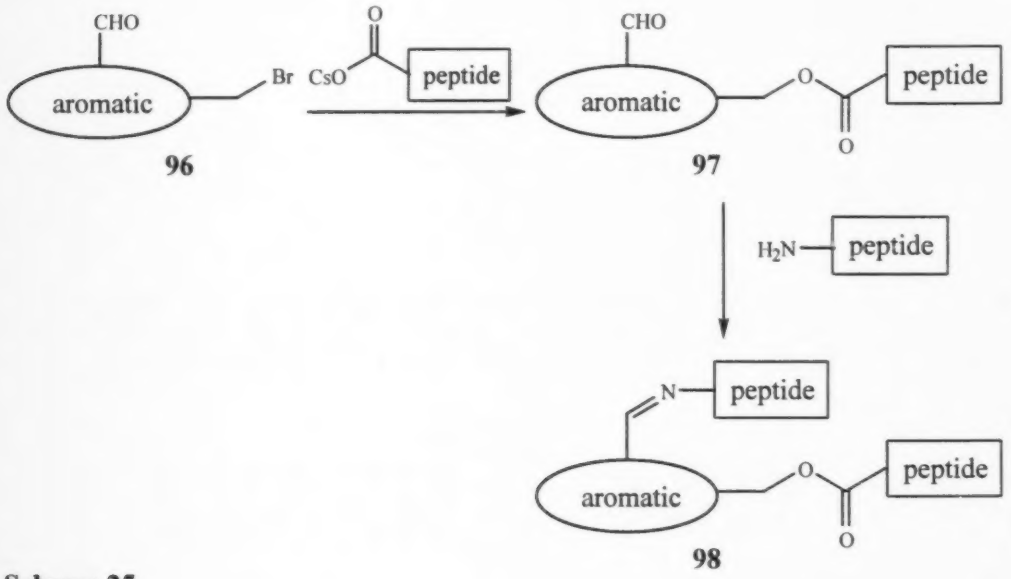
Scheme 24

there are three other considerations that should be mentioned. The first of these concerns the status (primary or secondary) of the amine that is attacking the carbonyl during peptide bond formation. Intramolecular acyl transfer proceeds fastest when the attacking nitrogen is primary (see the methods of Schemes 16,[18] 19,[22] and 20[23]). As stated at the end of the introduction however, we wanted to develop a *general* method of coupling peptides that did not require the presence of a specific amino acid (i.e. a cysteine residue) at the amino terminus. As a consequence, all methods we wished to consider would involve a secondary nitrogen during *O*→*N* acyl transfer. Use of a secondary nitrogen would not be an impediment however, since Tam[20] had had success with acyl transfer involving a secondary nitrogen (Scheme 17).

The second factor to consider before discussing our syntheses is the ring size during intramolecular acyl transfer. The methods of Kent[22] (Scheme 19) and Tam[20,23] (Schemes 17 and 20) involve *O*→*N* acyl transfer through a 5- or 6-membered ring — ring sizes through which one expects, on the basis of general experience, fast and efficient transfer. However, the influence of ring size on the facility of transfer is not fully understood, and Kemp[18] achieved effective transfer through a 12-membered ring (Scheme 16). Kemp realized[18a,19] that if the template is sufficiently rigid, intramolecular transfer can proceed quickly through unconventional ring sizes. With this in

mind, we did not limit ourselves to studying only those acyl transfers which involve 5- or 6-membered rings.

The last aspect of our plan was the problem of how the amino terminus of one peptide chain could be brought into close proximity to the carboxyl terminus the other chain. One possible approach would involve aromatic templates that contained both an aldehyde and bromide group (*The Single Template Approach*, Scheme 25). Bromide displacement by the

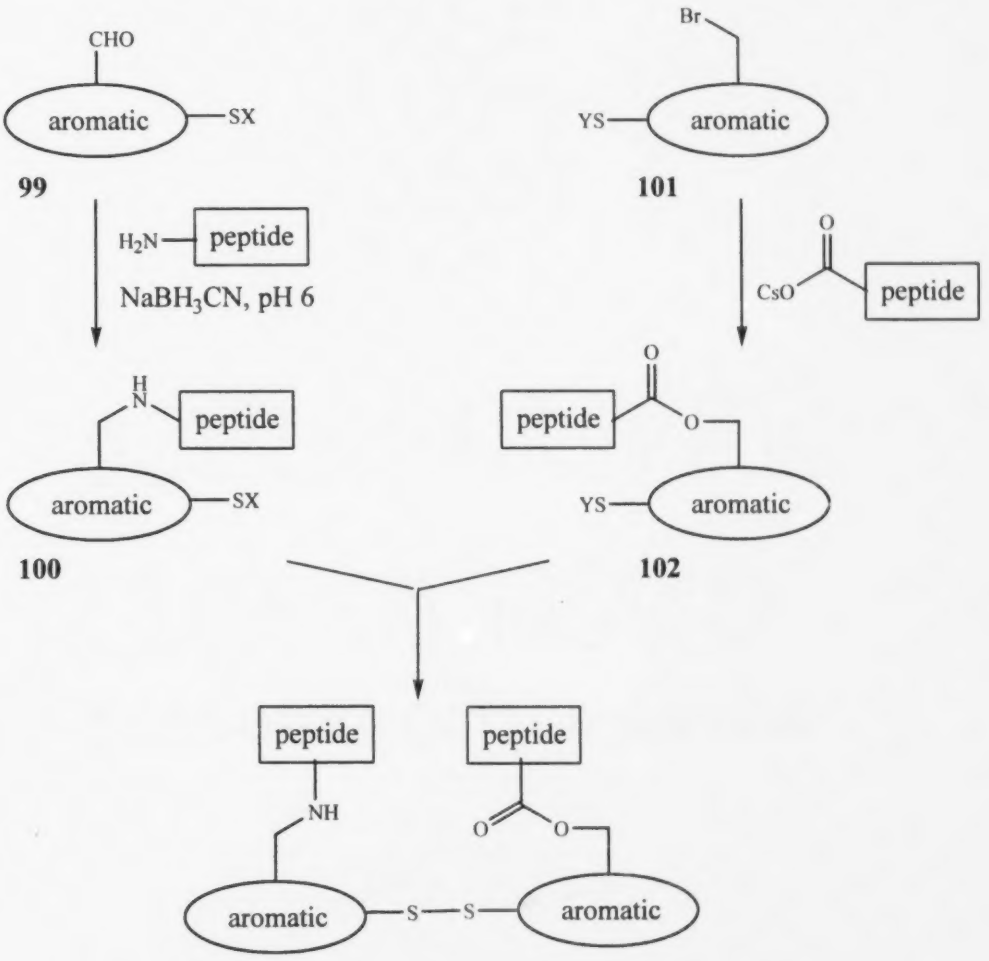


Scheme 25

carboxyl terminus on one peptide chain (**96**→**97**), followed by condensation of the aldehyde group with the amino terminus of another peptide chain (**97**→**98**) would result in formation of the desired imino-esters. Reduction of the imine to the corresponding amine, followed by *O*→*N* acyl transfer and

hydrogenolysis could then be completed, as discussed above.

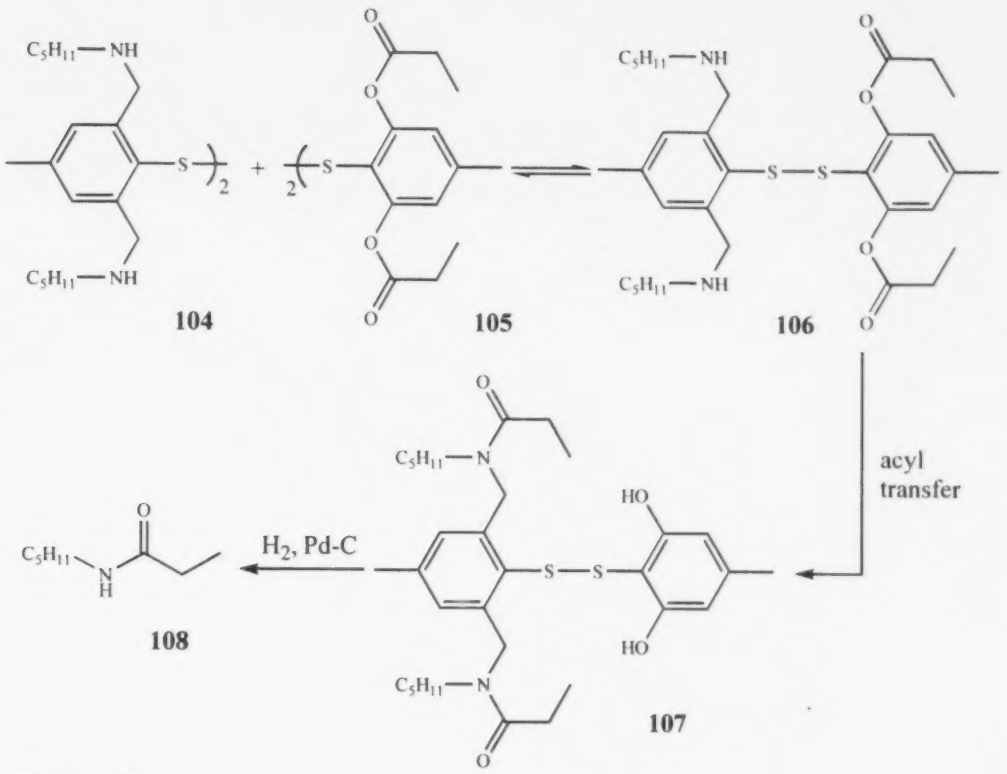
A second way of bringing the amino terminus of one peptide chain and the carboxyl terminus of another chain into close proximity involves the use of disulfides (*The Disulfide Approach*, Scheme 26). We planned to synthesize aromatic sulfides that contained an aldehyde group (**99**) or a



Scheme 26

bromomethyl group (**101**). Compound **99** would be converted into the corresponding imine and then reduced to the desired amine (**99**→**100**), while bromide displacement of compound **101** with the cesium salt of a carboxylic acid would give ester **102**. There are numerous ways of forming mixed disulfides,[26] and we hoped to find a method that would allow us to form our desired disulfide (**103**). With the amino terminus of one peptide chain and the carboxyl terminus of the other chain now in close proximity, *O*→*N* acyl transfer, and hydrogenolysis could proceed as described above. A closer examination of the two approaches just mentioned will now be given.

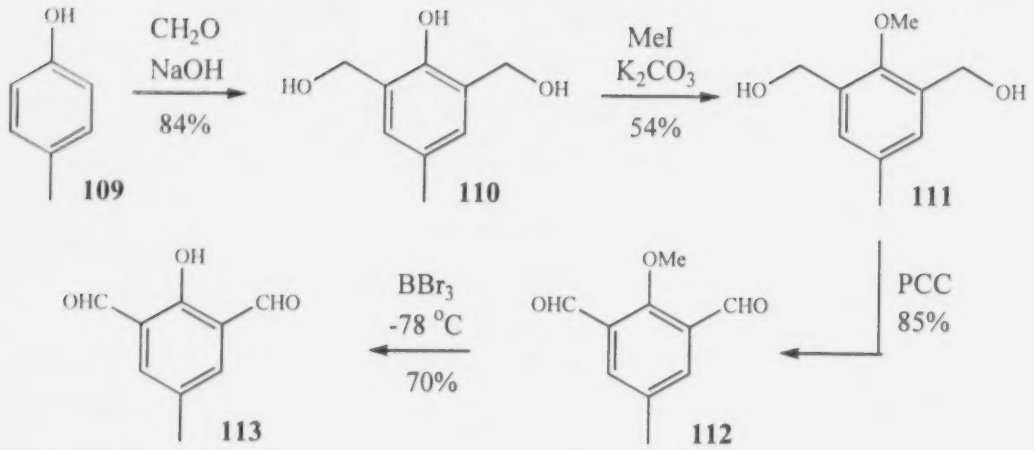
The Disulfide Approach: The first of the two main approaches to be discussed is the one that uses a disulfide link to bring the amino terminus of one peptide chain into close proximity to the carboxyl terminus another peptide chain (Scheme 27). We wanted to synthesize tetraamine disulfide **104** and tetra(propionate) disulfide **105**. The scrambling of two symmetrical disulfides to an equilibrium mixture of symmetrical and mixed disulfides has been well studied.[27] We hoped that when mixed disulfide **106** was formed, intramolecular acyl transfer (**106**→**107**) would proceed before the mixed disulfide scrambled again. Equilibration could continue until acyl transfer was



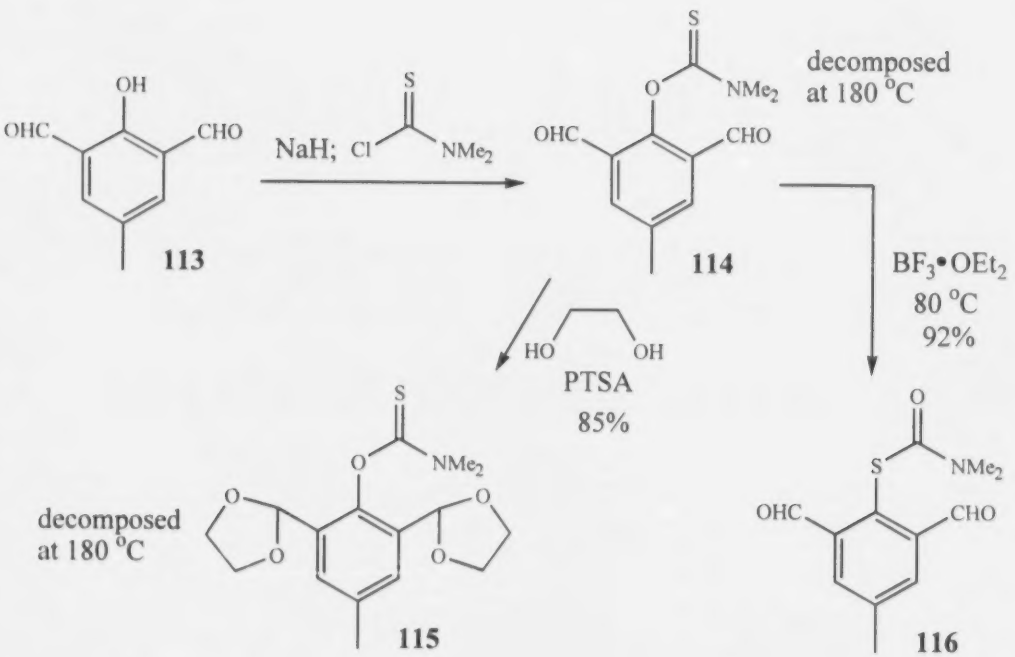
Scheme 27

complete, and then the newly formed amide would be cleaved from the template by hydrogenolysis (**107**→**108**).

Synthesis of disulfides **104** and **105** began with *p*-cresol (**109**) and proceeded through a modification of the route described by Ullmann and Brittner (Scheme 28).[28] *p*-Cresol (**109**) was converted into trihydroxy compound **110**, and then selective methylation gave the anisole derivative **111**. Oxidation of the primary hydroxyl groups furnished dialdehyde **112** and, finally, demethylation gave the phenolic dialdehyde **113**.



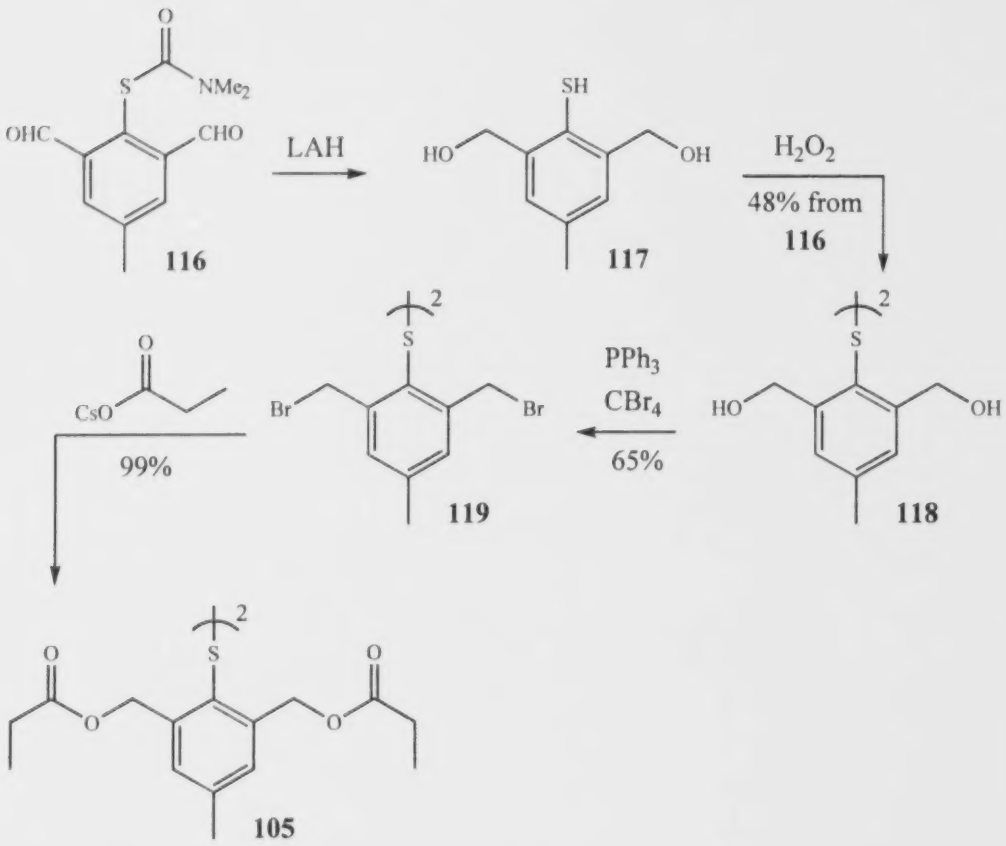
Scheme 28



Scheme 29

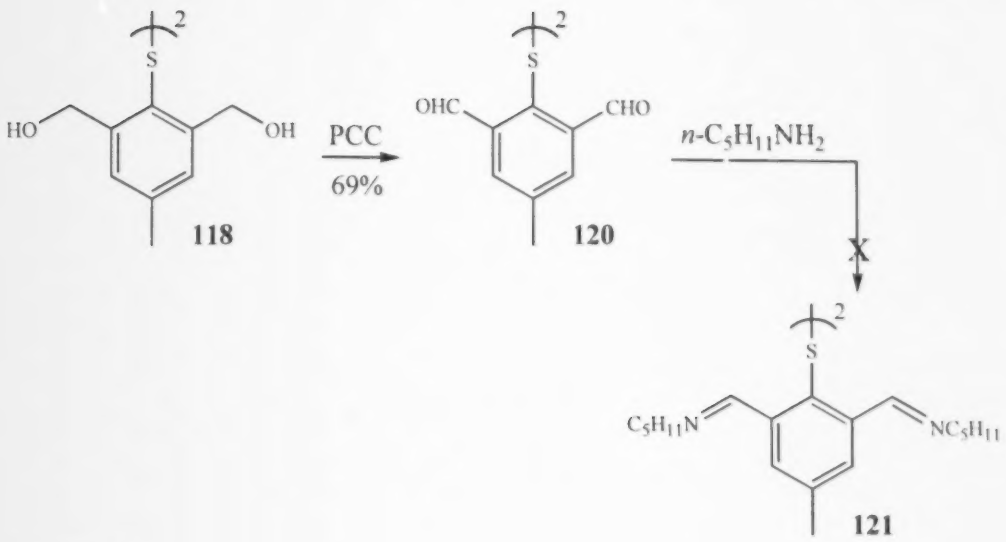
Phenol **113** was treated with dimethylthiocarbamoyl chloride[29] to produce the *O*-aryl thiocarbamate **114** (Scheme 29). Newman and Karnes had reported that *O*-aryl thiocarbamates undergo thermal rearrangement to *S*-aryl thiocarbamates[29] but, when thiocarbamate **114** was heated, the material decomposed. In an attempt to avoid this decomposition, compound **114** was converted into diacetal **115**, but once again, heating led to decomposition of the starting material. Fortunately, mild heating of *O*-aryl thiocarbamate **114** in the presence of $BF_3 \cdot OEt_2$ resulted in efficient formation of *S*-aryl thiocarbamate **116**. This compound was first reported in the literature by Robson[30] and more recently was used by Brooker.[31] Neither group reported a procedure or provided spectral data and, in discussions with the Brooker group, it became apparent that the $BF_3 \cdot OEt_2$ procedure, which was developed in our laboratory, was the most efficient.

Thiocarbamate **116** was reduced to thiol **117** and this was immediately oxidized to disulfide **118** (Scheme 30). Treatment of compound **118** with Ph_3P and CBr_4 led to the formation of tetra(bromide) **119**, and then displacement of the bromines by cesium propionate afforded the desired tetra(propionate) **105**.

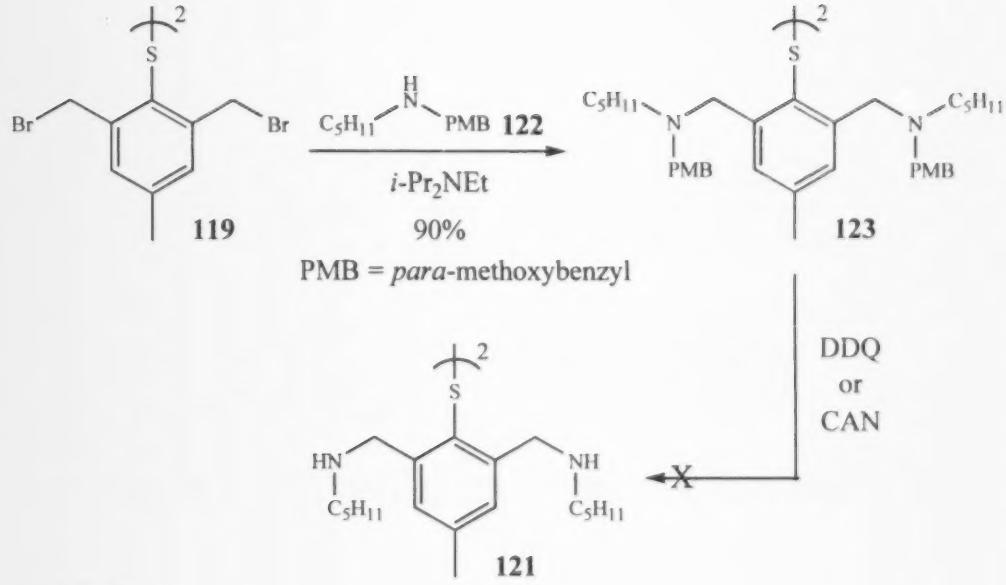


Scheme 30

While synthesis of tetra(propionate) **105** was relatively straightforward, isolation of tetraamine **104** (Scheme 27) was never accomplished. In one attempted route to **104** (Scheme 31), oxidation of tetra(hydroxy) compound **118** gave tetra(aldehyde) **120**. Unfortunately, treatment of this aldehyde **120** with amyl amine gave a mixture of compounds rather than the desired tetraimine **121**.



Scheme 31

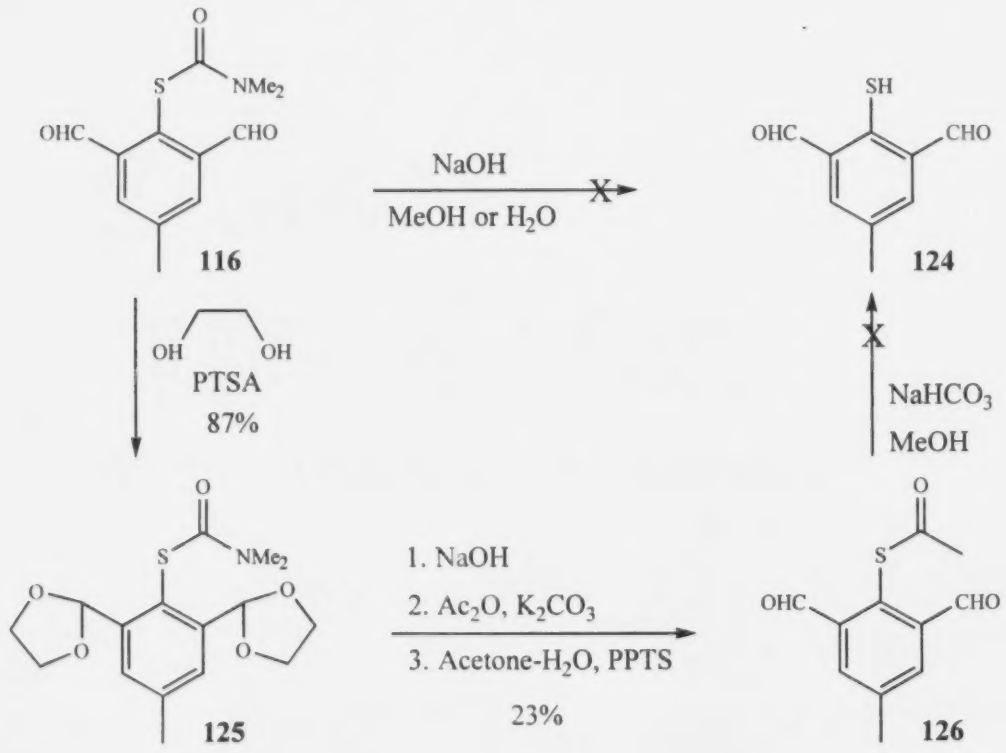


Scheme 32

In a second effort to synthesize tetraamine **104** (Scheme 32), tetrabromide **119** was reacted with (*p*-methoxybenzyl)(*n*-pentyl)amine (**122**), to give disulfide **123**. Attempts were

made, using CAN and DDQ, to remove the *p*-methoxybenzyl protecting groups, but these procedures were not successful. These last experiments failed to give the required tetraamine **104**, but we did not establish whether this was due to sensitivity of the disulfide group to the oxidizing conditions or whether the required amine did indeed form, but immediately underwent further reaction.[32]

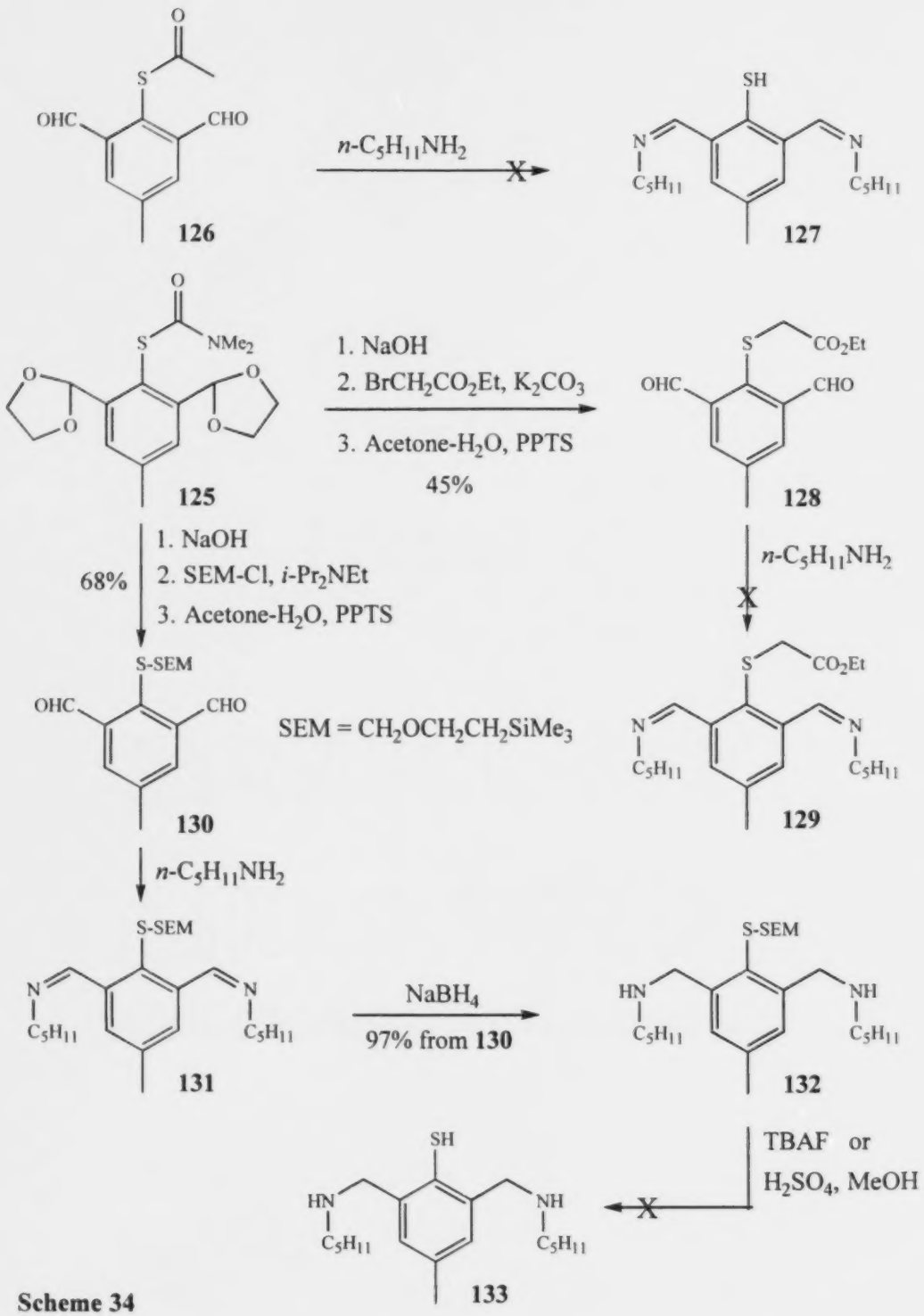
In further efforts at synthesizing tetraamine **104** we attempted to isolate thiophenol **124** from thiocarbamate **116** (Scheme 33). Treatment of compound **116** with aqueous or



Scheme 33

methanolic NaOH resulted in polymerization of the starting material. This was particularly annoying because generation of **124** in this way is actually reported in the literature;[31] however, contact with the authors eventually revealed that the compound had not actually been isolated — only used *in situ* — and that the wording in the literature was misleading. Next, a different procedure was investigated by first converting dialdehyde **116** into diacetal **125**. The thiocarbamate protecting group was removed, and replaced by an acetate and, finally, the aldehyde groups were deprotected, to give *S*-acetate **126**. This compound, even when treated under mild conditions such as methanolic $NaHCO_3$, polymerized, and we decided to make no further attempts to isolate thiophenol **124**.

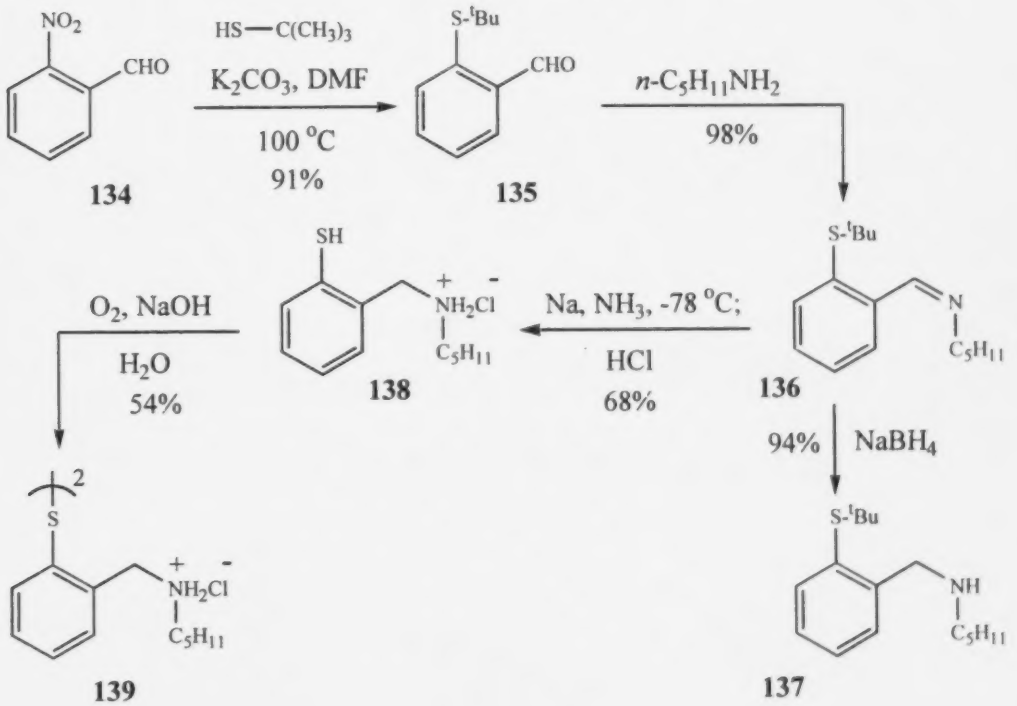
Instead of trying to synthesize compound **124**, we sought to bypass it en route to diamine **133** (Scheme 34). In one attempt, *S*-acetate **126** was reacted with amyl amine, but instead of obtaining diimine **127**, a thiazole system was formed.[32] In another effort, diacetal **125** was converted into the ethyl thioacetate **128**. Once again, treatment with amyl amine did not yield the desired diimine (**129**), and only a complex mixture was obtained. Finally, diacetal **125** was transformed into *S*-SEM-protected dialdehyde **130**. This time, treatment with amyl amine led to formation of the desired


126
n-C5H11NH2
127
125
1. NaOH
2. BrCH2CO2Et, K2CO3
3. Acetone-H2O, PPTS
45%
128
68%
1. NaOH
2. SEM-Cl, i-Pr2NEt
3. Acetone-H2O, PPTS
n-C5H11NH2
SEM = CH2OCH2CH2SiMe3
130
129
n-C5H11NH2
131
NaBH4
97% from 130
132
TBAF or
H2SO4, MeOH
133

Scheme 34

diimine (**131**). Reduction of diimine **131** to diamine **132** proceeded smoothly, but all attempts to remove the SEM protecting group were unsuccessful, and we were not able to establish what course the reaction was taking. At this point, plans to synthesize tetraamine **104** using variations of the routes discussed above were abandoned.

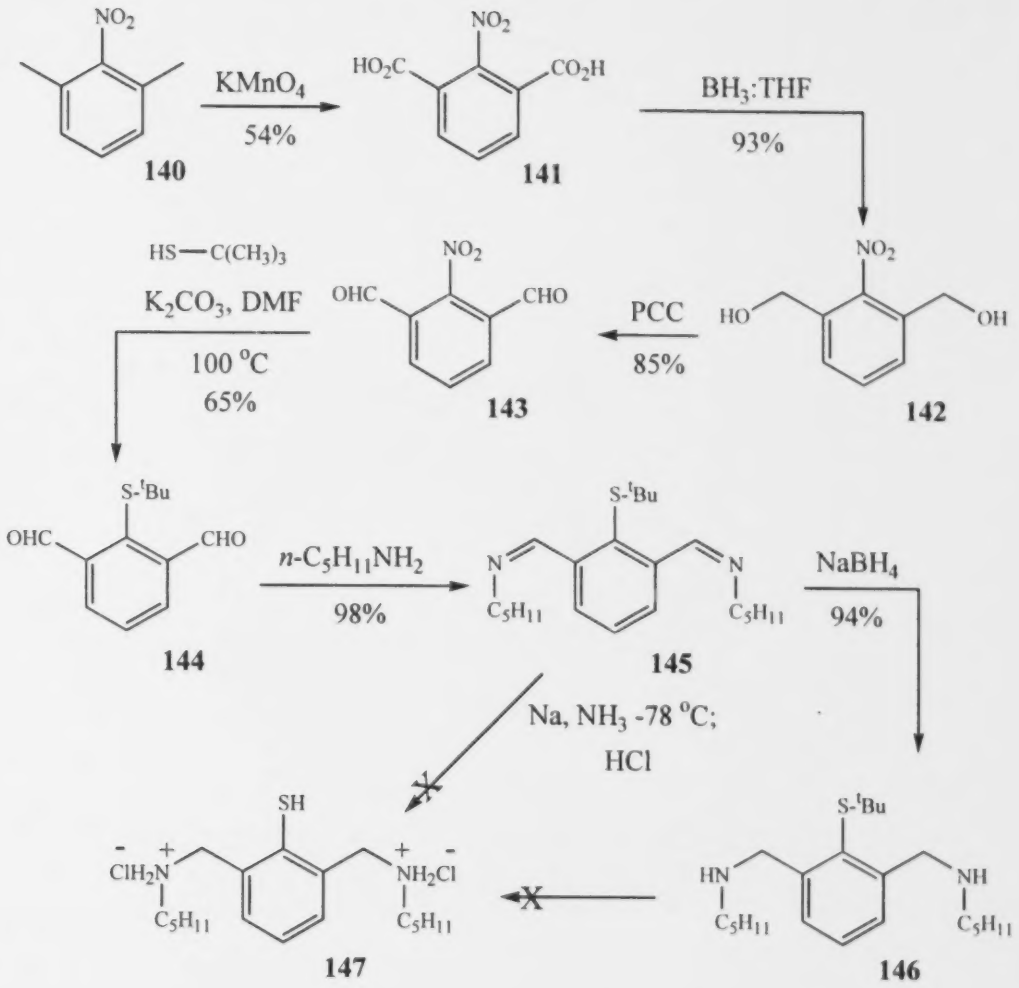
An alternative approach to *o*-thiobenzylamines was now investigated (Scheme 35). Thioether **135** was made from nitrobenzene **134**, using the procedure of Meth-Cohn and Tarnowski.[33] The aldehyde group of compound **135** was



Scheme 35

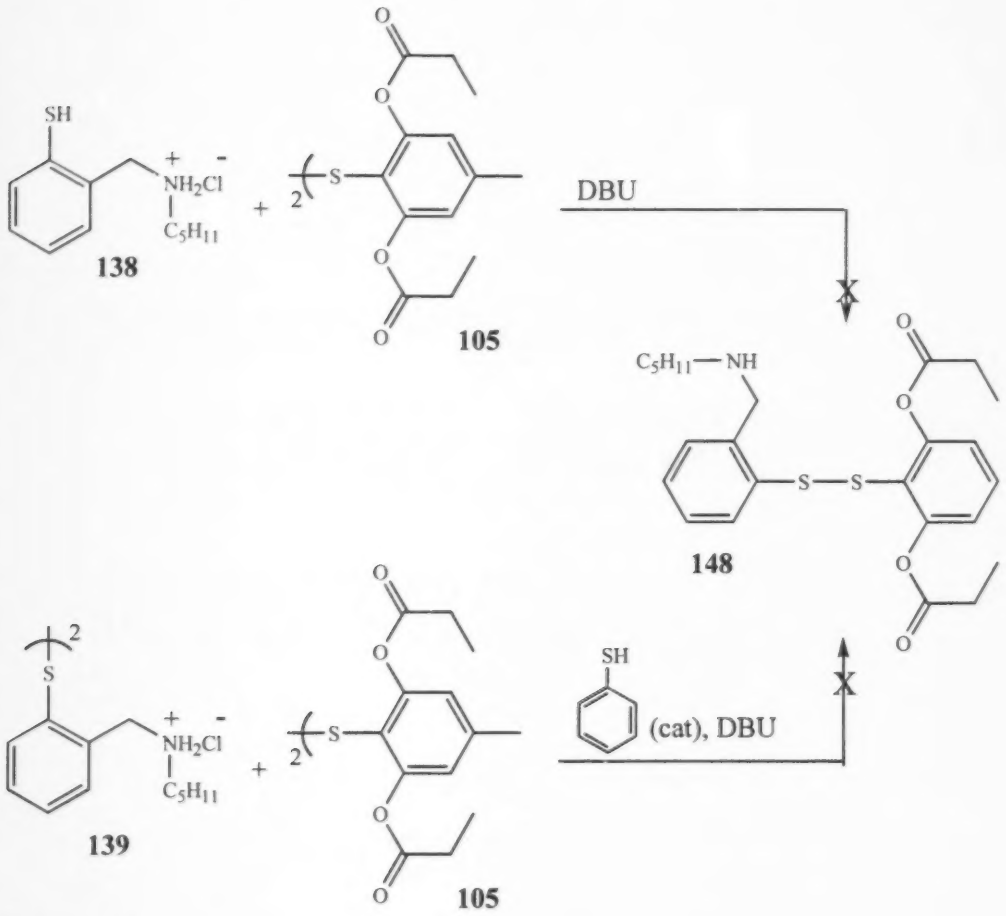
condensed with amyl amine to give imine **136**. Reduction of imine **136** to amine **137** went as expected, but all attempts to remove the *t*-butyl protecting group were unsuccessful. Fortunately, when imine **136** was reacted with sodium in liquid ammonia,[34] followed by acidic work-up, HCl-salt **138** was isolated in acceptable yield. Oxidation of compound **138**, in basic medium, followed by acidification, resulted in formation of disulfide **139**.

In addition to the preparation of thiol **138**, we also attempted to make thiol **147** (Scheme 36). The xylene **140** was converted into diacid **141**, using a modification of the procedure of Notting and Gachot.[35] Reduction to diol **142**, followed by oxidation to dialdehyde **143**,[36] proceeded smoothly, and then compound **143** was transformed into thioether **144**. Treatment of compound **144** with amyl amine afforded diimine **145**, and reduction of this material furnished diamine **146**. Unfortunately, neither compound **145** nor **146** could be converted into **147**, and so we had only amines **138** and **139** (Scheme 35) to use in disulfide exchange experiments.



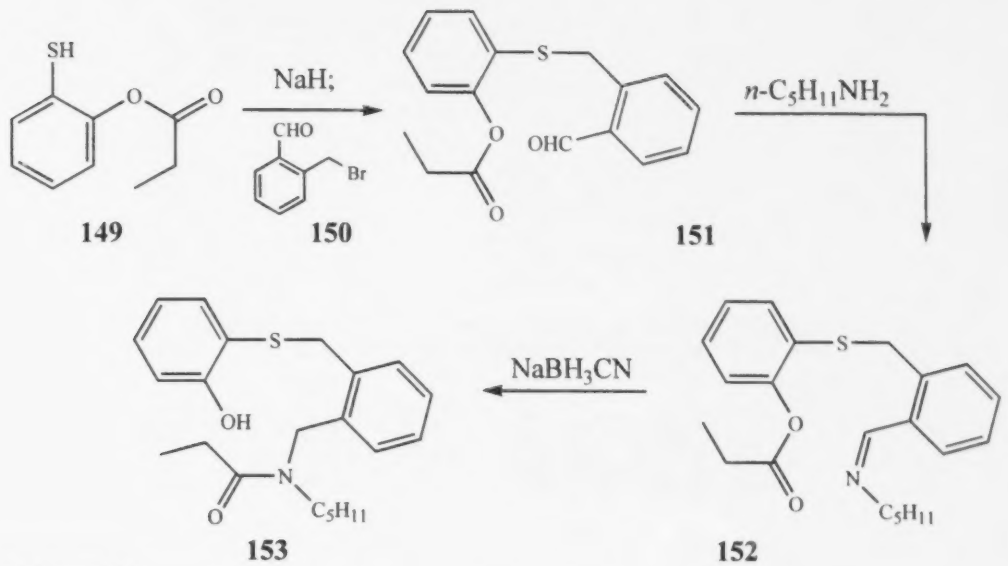
Scheme 36

Several attempts were made (Scheme 37) to make mixed disulfide **148** by reacting thiol **138** with tetra(propionate) **105**, or by equilibrating disulfides **105** and **139**. However, no evidence of amide bond formation (^{1}H NMR, FTIR) or mixed disulfide formation (^{1}H NMR) was seen. While much work has been reported on thiolate-disulfide interchange of alkyl thiols,[27] there is little information on exchange between



Scheme 37

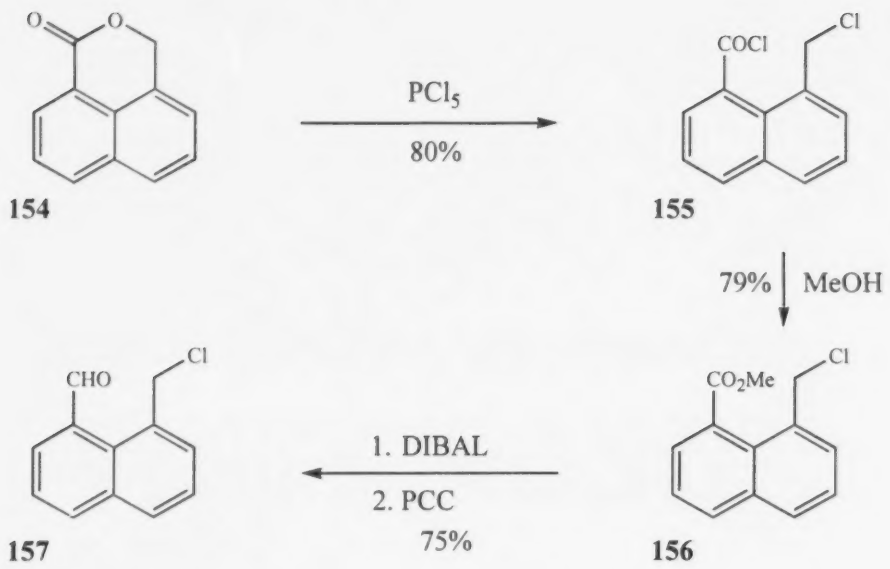
aryl disulfides.[27c] The mechanism of interchange involves nucleophilic attack of the thiolate anion along the S—S bond axis of the disulfide,[37] but possibly, the *ortho*-substitution on the aryl rings renders the S—S bond axis inaccessible to the thiolate anion. Model studies using phenyl disulfide and *p*-methylphenyl disulfide would help determine whether aryl disulfide exchange in simpler systems occurs easily.



Scheme 38

If a lack of disulfide exchange is the problem with the design illustrated in Scheme 37, then it would still be instructive to consider whether *O→N* acyl exchange occurs for the ring size implied by the Scheme. A possible control experiment (which we have not yet tried) is shown in Scheme 38. Thiol **149** would be linked to aldehyde **150**, forming thioether **151**. The aldehyde would be converted into an imine (**151→152**) and then, hopefully, reduction of the imine to the corresponding amine would be followed by intramolecular acyl transfer, giving amide **153**.

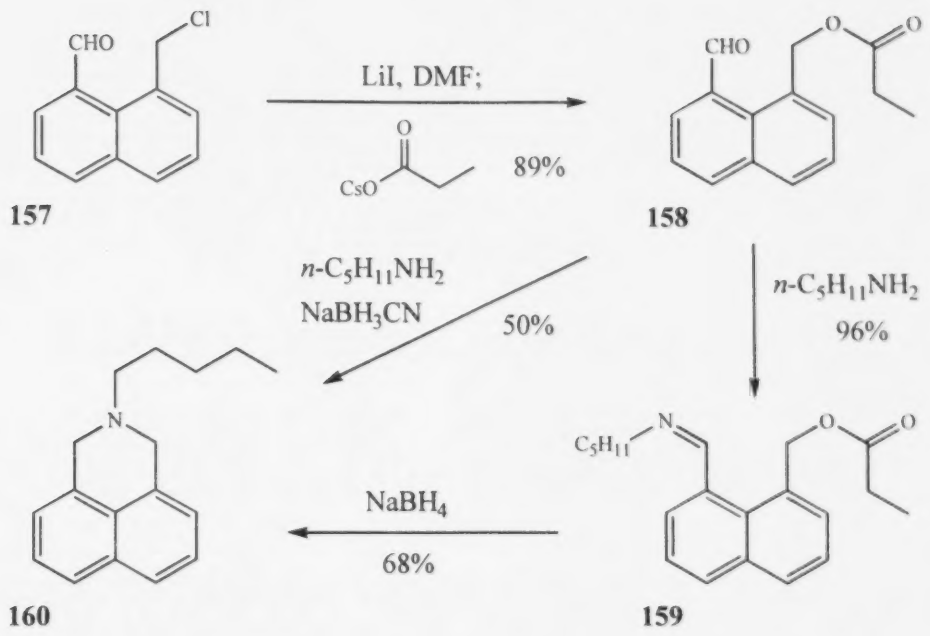
The Single Template Approach: The first template of this class that we investigated was chloromethyl naphthaldehyde **157** (Scheme 39). Synthesis of this compound



Scheme 39

was accomplished by first converting the known lactone **154**[38] into acid chloride **155** using PCl_5.[39] The acid chloride was transformed into the corresponding methyl ester (**155**→**156**) and then a reduction-oxidation procedure gave the desired template (**157**).

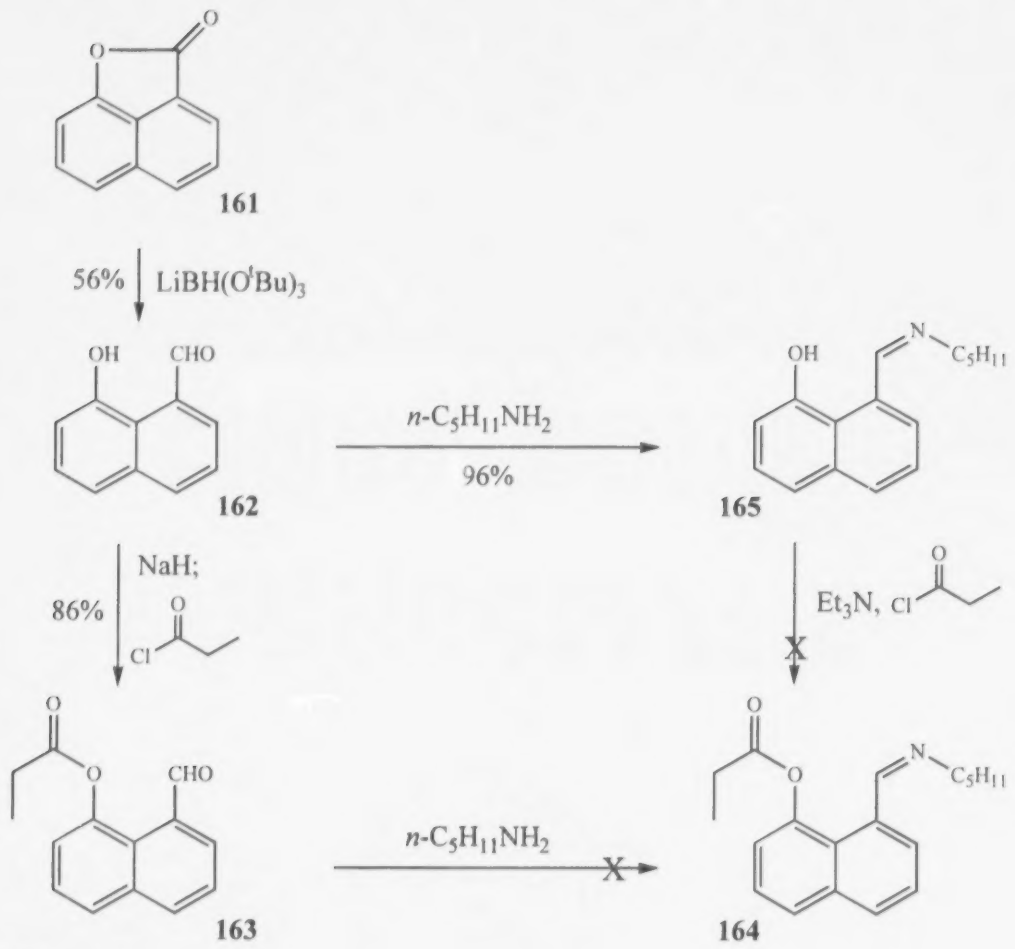
With template **157** constructed, we proceeded by displacing the chlorine with cesium propionate, to afford ester aldehyde **158** (Scheme 40). The aldehyde group was condensed with amyl amine, giving imine **159**. The amino group was now in close proximity to the carbonyl group and we were ready to attempt intramolecular *O*→*N* acyl transfer. With this system, acyl transfer would proceed through an 8-membered ring, and although such processes are uncommon in



Scheme 40

acyclic systems, we hoped that the rigidity of the template would make our desired transfer more favorable. Unfortunately, when imine **159** was reduced with $NaBH_4$, tertiary amine **160** was isolated as the major product. Similarly, when aldehyde **158** was reacted with amyl amine in the presence of $NaBH_3CN$,[40] amine **160** was the only product isolated. It appears that the template strongly favors formation of a 6-membered ring, and displacement of the propionate group (giving amine **158**) is much easier than the desired acyl transfer pathway.

The next template we wanted to study was naphthaldehyde **162**, which had previously been studied by Kemp.[41] Compound

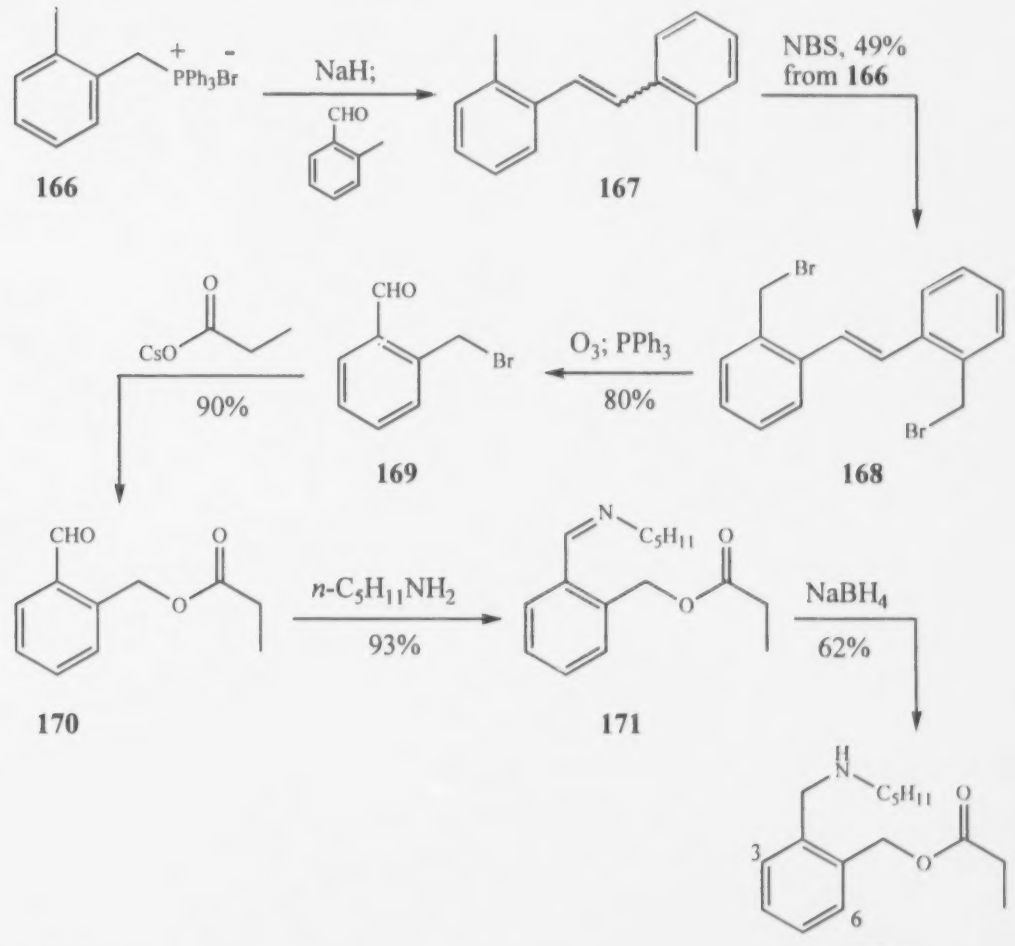


Scheme 41

162 was synthesized from lactone **161** using the procedure of Elliger[42] (Scheme 41). Acylation of naphthol **162** afforded propionate **163**. The aromatic ester in compound **163** is weakly activated (relative to an aliphatic ester), and this activation caused problems when compound **163** was reacted with amyl amine. Rather than selectively forming imine **164**, the ester competed with the aldehyde for the nucleophilic

amine, resulting in a mixture of products, as observed by Kemp. In an attempt to circumvent this problem, aldehyde **162** was reacted with amyl amine, furnishing imine **165**. Surprisingly, the expected acylation of the hydroxyl group did not occur, and we were unable to obtain the desired iminoester **164** by acylation of naphthol **165**.

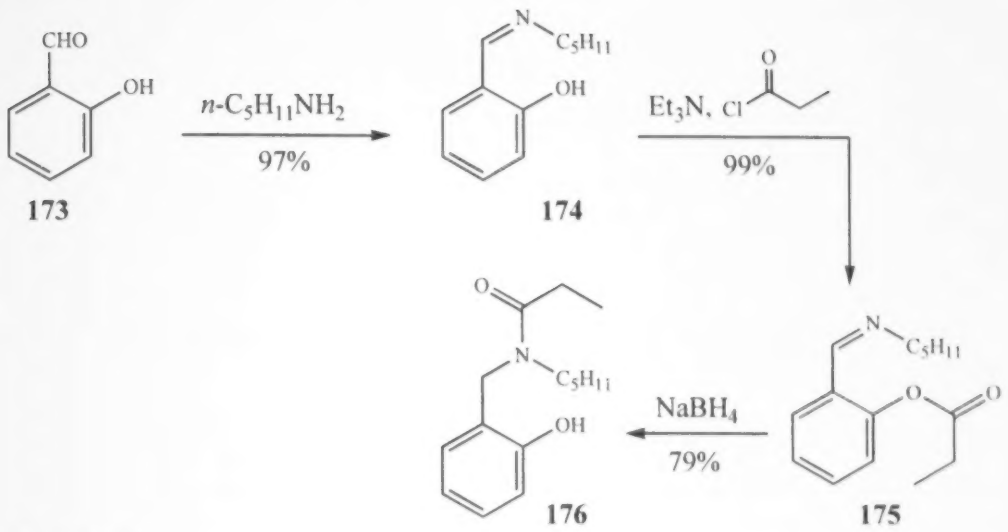
The third template we considered was *o*-(bromomethyl)-



Scheme 42

benzaldehyde (**169**) (Scheme 42). Synthesis of compound **169** began by coupling phosphonium salt **166** and o-tolualdehyde to form symmetrical olefin **167** as a mixture of stereoisomers. The mixture was treated with NBS under photolysis conditions to afford dibromide **168**, and then ozonolysis gave the desired template **169**. Bromide displacement from compound **169** with cesium propionate furnished ester **170**, and treatment with amyl amine then gave imine **171**. Compound **171** was reacted with $NaBH_4$ giving amine **172**. No acyl transfer, which would have proceeded through a 7-membered ring, was observed (during a 3-hour reaction period). In retrospect, we think that a template having methyl (or ethyl) substituents at positions 3 and 6 (in **172**) might have a higher population of conformations in which the nitrogen and carbonyl units are close.

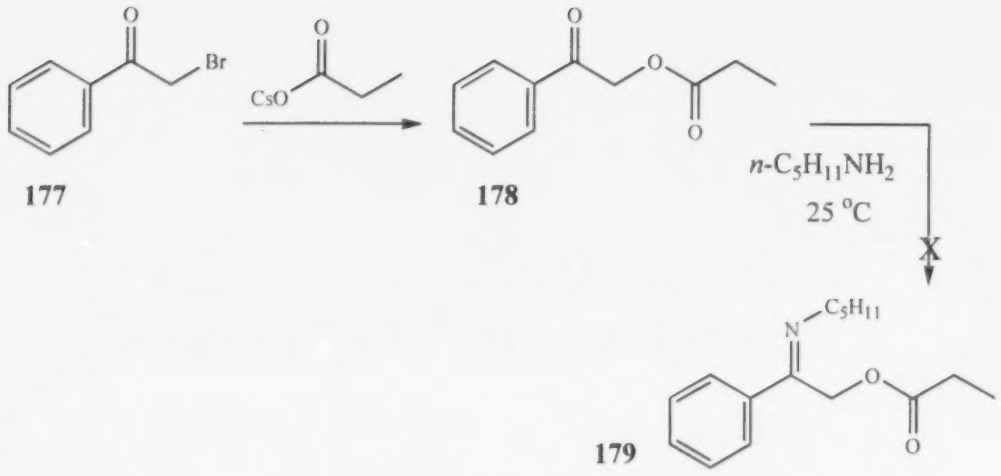
The fourth template we considered was salicylaldehyde (**173**), which was first converted into imine **174**, using standard conditions, and then was acylated, affording propionate **175** (Scheme 43). When compound **175** was treated with $NaBH_4$, reduction of the imine was followed by intramolecular acyl transfer, through a 6-membered ring, to give amide **176**. While it was gratifying to make a peptide bond, this system has a significant flaw. Because the template is a phenol, the key ester linkage must be made using acylating conditions. Linking a long peptide chain to



Scheme 43

the phenol would require activation of the carboxyl terminus and this would lead to racemization[4,5] of the carbon α to the carboxyl terminus. As a result of this flaw, template **173** was not considered further. Related observations by Kemp[19] have also not been followed up.

We next wanted to consider a system that would involve intramolecular acyl transfer through a 5-membered ring. A natural extension of the templates we had studied earlier would involve α-bromo ketone **177** (Scheme 44). While bromide displacement, giving propionate **178** proceeded smoothly, imine formation leading to compound **179** did not. Unlike imine formation using aldehydes, Schiff base synthesis using ketones[24] requires heating and azeotropic removal of water. As a result, templates containing a ketone group could not be used, even, as is the case in our

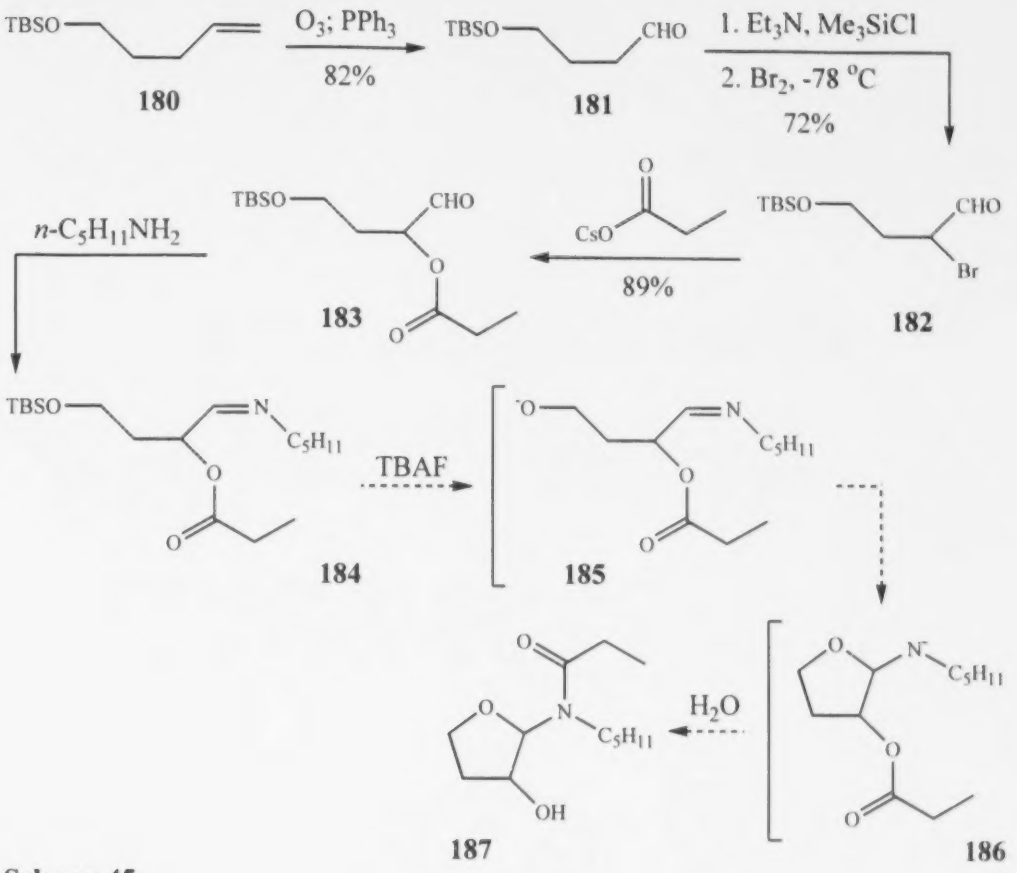


177 178 179

Scheme 44

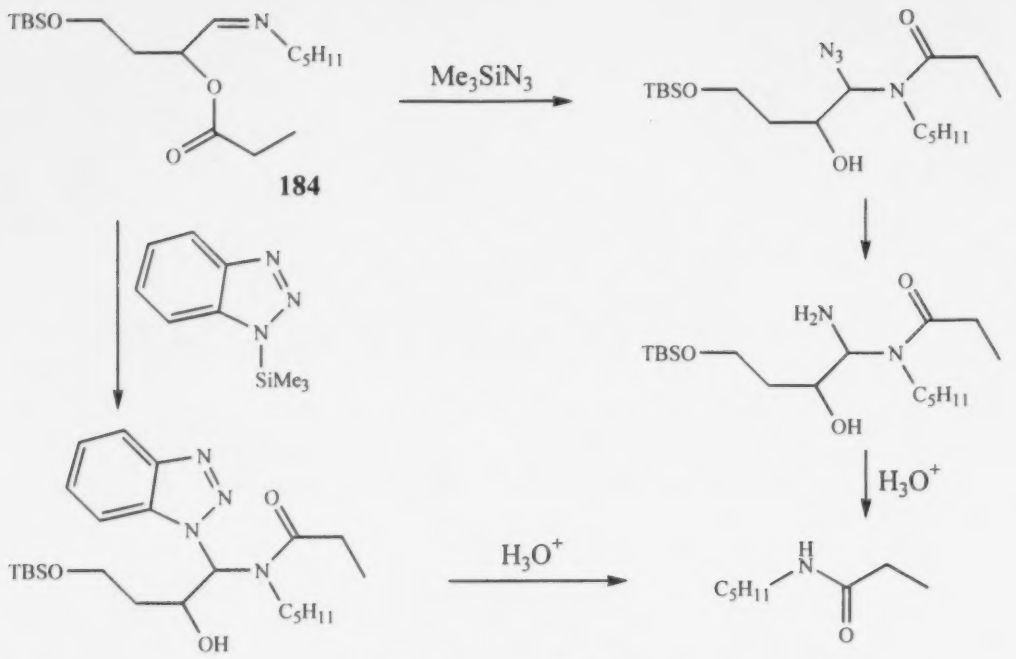
substrates, when an electron-withdrawing group flanks the carbonyl.

At this point, we needed to alter our general approach. We wanted to retain the bromine and aldehyde groups in the template, but the new design did not require imine reduction with $NaBH_3CN$ or the presence of an aryl group. Synthesis of our desired template (**182**) began with ozonolysis of olefin **180** to give aldehyde **181** (Scheme 45). The aldehyde was converted into the corresponding silyl enol ether,[43] and then reacted with Br_2[44] so as to afford template **182**. Displacement of the secondary bromide proceeded smoothly to give propionate **183**, and then imine **184** was formed using standard conditions. When compound **184** was reacted with TBAF, an unstable product was formed. The substance has not yet been identified, but the reaction is being examined



Scheme 45

further. Our hope is that alkoxide **185** that is released will cyclize (**185→186**) so as to form a species that should undergo *O→N* acyl transfer (**186→187**). Should this not occur, we plan to examine the modified version of this acyclic template approach summarized in Scheme 46.



Scheme 46

Conclusions:

The design of a template that can bring the carboxyl terminus and the amino terminus of different peptide chains into close proximity, so that intramolecular coupling occurs, is clearly an extremely complex task, especially if, as in the present case, a general approach is sought. Our experiments have led us to regard processes of the type summarized in Schemes 45 and 46 as very worthy of serious consideration, and work along those lines is in hand.

Experimental:

General experimental procedures were the same as those used previously (see Chapter 1).

2,6-Bis(hydroxymethyl)-4-cresol (110).

109 **110**

The literature procedure[28] was modified. Aqueous formaldehyde (39% w/v, 46.2 g, 600 mmol) was added to a stirred solution of phenol **109** (23.18 g, 214 mmol) in aqueous NaOH (6 M, 45 mL). Stirring was continued for *ca.* 7 h until a solid mass had formed, and this mixture was left for another 20 h. The solid was collected, rinsed with cold (0 °C) brine (40 mL), and dissolved in water (450 mL). The solution was acidified with aqueous AcOH (20% v/v). The mixture was cooled to 0 °C and the resulting crystals were collected. The crude material was recrystallized from a mixture of EtOAc and acetone to give triol **110** (30.22 g 84%) as a pure (^{1}H NMR, 300 MHz) white solid: FTIR (acetone cast) 3395, 3310 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.19 (s, 3 H), 4.71 (s, 4 H), 5.20-6.26 (br s, 2 H), 6.90 (s, 2 H), phenolic O-*H* was not detected; ^{13}C NMR (75.5 MHz, acetone-d_6) δ 20.57 (q'), 62.24 (t'), 127.58 (s' and d'), 128.53 (s') 152.42

(s'); exact mass *m/z* calcd for $C_9H_{12}O_3$ 168.07864, found 168.07874.

2,6-Bis(hydroxymethyl)-4-methylanisole (111).

110 **111**

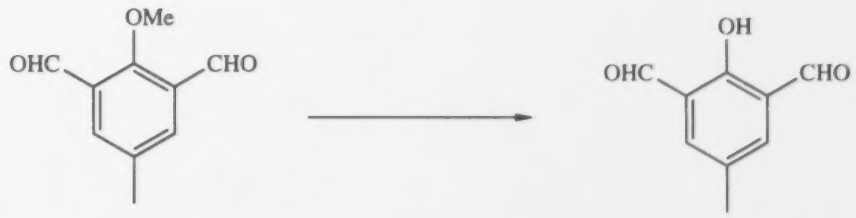
MeI (12.4 mL, 200 mmol) was added to a warmed (45 °C) and stirred mixture of triol **110** (10.61 g, 63.0 mmol) and K_2CO_3 (11.1 g, 80.0 mmol) in acetone (120 mL). Stirring was continued for 12 h, the solvent was evaporated, and the residue was dissolved in EtOAc (600 mL) and water (400 mL). The layers were separated and then the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from a mixture of hexanes and acetone to give diol **111** (6.23 g, 54%) as a pure (^1H NMR, 300 MHz) white solid: FTIR (CH_2Cl_2 cast) 3266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.13 (t, *J* = 6.0 Hz, 2 H), 2.32 (s, 3 H), 3.85 (s, 3 H), 4.14 (d, *J* = 6.0 Hz, 4 H), 7.15 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.81 (q'), 60.95 (t'), 62.23 (q'), 129.51 (d'), 133.63 (s'), 134.31 (s'), 153.93 (s'); exact mass *m/z* calcd for $C_{10}H_{14}O_3$ 182.09430, found 182.09454.

2,6-Diformyl-4-methylanisole (112).

111 **112**

PCC (30.7 g, 142 mmol) was added to a stirred mixture of diol **111** (8.66 g, 47.5 mmol) and molecular sieves (4 Å, 31 g) in CH_2Cl_2 (350 mL). Stirring was continued for 6 h and then the mixture was filtered through a pad (4 x 4 cm) of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (5.5 x 30 cm), using CH_2Cl_2, gave dialdehyde **112** (7.25 g, 85%) as a pure (^{1}H NMR, 300 MHz), white solid. FTIR (CH_2Cl_2 cast) 2863, 2783, 1683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 4.05 (s, 3 H), 7.90 (s, 2 H), 10.38 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.59 (q'), 66.80 (q'), 129.75 (s'), 135.03 (s'), 135.44 (d'), 163.65 (s'), 188.64 (d'); exact mass *m/z* calcd for $C_{10}H_{10}O_3$ 178.06299, found 178.06280.

2,6-Diformyl-4-cresol (113).



112 **113**

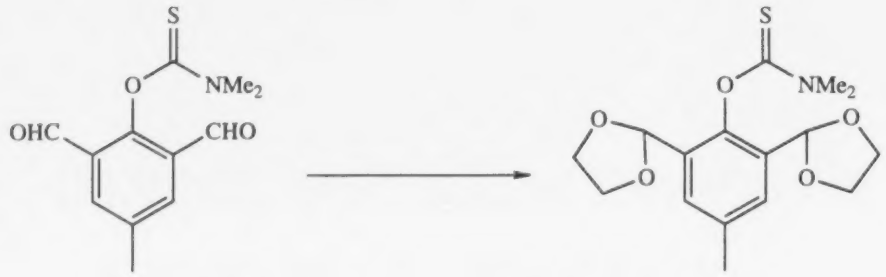
BBr_3 (3.79 mL, 40.0 mmol) was added dropwise over *ca.* 5 min to a cooled (-78 °C) and stirred solution of ether **112** (6.64 g, 37.3 mmol) in CH_2Cl_2 (100 mL). The cold bath was removed and stirring was continued for 12 h. The reaction was quenched with water (200 mL). The aqueous layer was extracted with EtOAc (2 x 150 mL), and then the combined organic extracts were washed with aqueous NaOH (10% w/v, 3 x 150 mL). The combined basic aqueous washings were acidified and then extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 x 20 cm), using 15% EtOAc-hexane, gave phenol **113** (4.28 g, 70%) as a pure (^1H NMR, 300 MHz), yellow solid: FTIR (CH_2Cl_2 cast) 2870, 1681, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 7.77 (s, 2 H), 10.22 (s, 2 H), 11.45 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.14 (q'), 122.96 (s'), 129.57 (s') 138.02 (d'), 168.82 (s'), 192.25 (d'); exact mass *m/z* calcd for $C_9H_8O_3$ 164.04735, found 164.04736.

2-[*O*-(*N*,*N*-Dimethylthiocarbamoyl)]-5-methylisophthal-aldehyde (114).

113 **114**

NaH (36.0 mg, 1.50 mmol) was added to a cooled (0°C) and stirred solution of phenol **113** (134.7 mg, 0.821 mmol) in DMF (5 mL). The resulting orange mixture was stirred for 30 min and then dimethylthiocarbamoyl chloride (371 mg, 3.00 mmol) was added. The mixture was heated (80 °C) and stirred for 1.5 h. The solution was cooled, diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave thiocarbamate **114** (179.3 mg, 87%) as a pure (^1H NMR, 300 MHz), cream solid: FTIR (CH_2Cl_2 cast) 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 3.49 (s, 3 H), 3.50 (s, 3 H), 7.94 (s, 2 H), 10.08 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.78 (q'), 39.21 (q'), 43.70 (q'), 129.88 (s'), 135.60 (d'), 137.11 (s'), 154.39 (s'), 186.90 (s'), 187.62 (d'); exact mass *m/z* calcd for $C_{12}H_{13}O_3NS$ 251.06161, found 251.06137.

2-[*O*-(*N*,*N*-Dimethylthiocarbamoyl)]-5-methylisophthalaldehyde bis(ethylene acetal) (115).



114 **115**

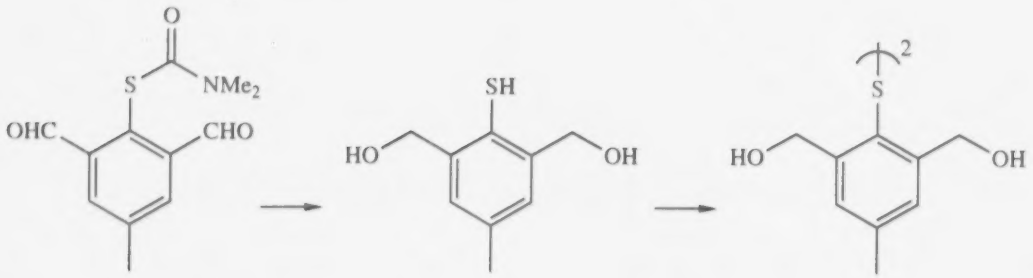
Ethylene glycol (6.21 g, 100 mmol) and PTSA (19 mg, 0.10 mmol) were added to a warmed (60 °C) and stirred solution of dialdehyde **114** (162.2 mg, 0.645 mmol) in PhH (20 mL). The oil bath temperature was increased to 115 °C, and the system was refluxed through a Soxhlet apparatus containing a thimble filled with CaH_2. After 1.5 h, the solution was cooled to room temperature, diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 50% EtOAc-hexane, gave diacetal **115** (187.6 mg, 85%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1538, 1396, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 3.39 (s, 3 H), 3.45 (s, 3 H), 3.91-4.17 (m, 8 H), 5.92 (s, 2 H), 7.42 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.24 (q'), 38.79 (q'), 43.46 (q'), 65.01 (t'), 65.34 (t'), 99.65 (d'), 128.41 (d'), 131.06 (s'), 135.91 (s'), 148.21 (s'), 186.87 (s'); exact mass *m/z* calcd for $C_{14}H_{17}O_3NS$ (M^+-$C_2H_4O_2$) 279.09293, found 279.09276.

2-[*S*-(*N*,*N*-Dimethylthiocarbamoyl)]-5-methylisophthalaldehyde (116).

114 **116**

$BF_3 \cdot OEt_2$ (0.12 mL, 1.00 mmol) was added to a warmed (60 °C) and stirred solution of thiocarbamate **114** (1.26 g, 5.03 mmol) in PhH (30 mL). The oil bath temperature was increased and the mixture was refluxed for 8 h. The solution was allowed to cool and then evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 30% EtOAc-hexane, gave thiocarbamate **116** (1.17 g, 92%) as a pure (^{1}H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1689, 1664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 3.04 (s, 3 H), 3.36 (s, 3 H), 8.03 (s, 2 H), 10.53 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.14 (q'), 37.32 (q'), 37.47 (q'), 131.95 (s'), 134.11 (d'), 138.34 (s'), 141.12 (s'), 163.89 (s'), 190.46 (d'); exact mass *m/z* calcd for $C_{12}H_{13}O_3NS$ 251.06161, found 251.06125.

Bis[2,6-bis(hydroxymethyl)-4-methylphenyl]disulfide (118).



116 **117** **118**

A solution of thiocarbamate **116** (1.85 g, 7.36 mmol) in THF (20 mL plus 10 mL as a rinse) was added to a cooled (0 °C) and stirred suspension of LAH (959 mg, 24.0 mmol) in THF (70 mL). The cold bath was removed, and stirring was continued for 30 min. The reaction was quenched carefully with water (200 mL) and the mixture was then acidified to pH 2, using aqueous HCl (1 M). The product was extracted with EtOAc (3 x 100 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give crude (TLC control, silica, EtOAc) thiophenol **117**.

The crude thiophenol **117** was dissolved in a solution of MeOH (30 mL) and aqueous water (30% w/v, 25 mL), and the mixture was stirred for 48 h. The mixture was diluted with EtOAc (300 mL), washed with brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from acetone to give disulfide **118** (649 mg, 48%) as a white solid containing trace impurities (^{1}H NMR, 300 MHz): FTIR (acetone cast) 3360 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 6 H), 4.36 (d, J =

5.5 Hz, 8 H), 5.08 (t, J = 5.5 Hz, 4 H), 7.23 (s, 4 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.35 (q'), 60.69 (t'), 125.95 (s'), 126.12 (d'), 139.48 (s'), 145.90 (s'); exact mass m/z calcd for $C_9H_{10}O_2S$ (M^+-$C_9H_{12}O_2S$) 182.04015, found 182.04030.

Bis[2,6-bis(bromomethyl)-4-methylphenyl]disulfide (119).

118 **119**

Ph_3P (2.62 g, 10.0 mmol) and CBr_4 (3.32 g, 10.0 mmol) were added successively to a stirred mixture of tetraol **118** (364.2 mg, 0.944 mmol) in CH_2Cl_2 (60 mL). Stirring was continued for 8 h and then the mixture was filtered through a pad (3.5 x 4 cm) of silica gel, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 25 cm), using 10% EtOAc-hexane, gave tetrabromide **119** (402.4 mg, 65%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 6 H), 4.38 (s, 8 H), 7.26 (s, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.25 (q'), 31.63 (t'), 131.19 (s'), 132.37 (d'), 141.72 (s'), 143.23 (s'); exact mass m/z calcd for $C_{18}H_{18}{}^{79}Br_4S_2$ 613.75836, found 613.75815.

Bis[[2,6-bis[(propionyloxy)methyl]-4-methylphenyl]]-disulfide (120).

119 **120**

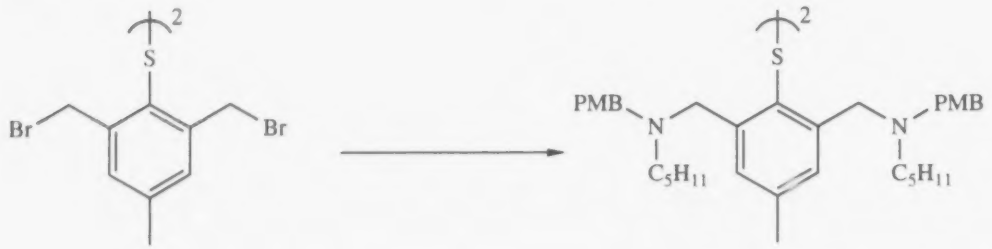
Cesium propionate (824 mg, 4.00 mmol) was added to a stirred solution of tetrabromide **119** (419.0 mg, 0.678 mmol) in DMF (15 mL). Stirring was continued for 1 h and then the mixture was diluted with EtOAc (100 mL). The solution was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 20% EtOAc-hexane, gave tetra(propionate) **120** (396.2 mg, 99%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1740, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.5 Hz, 12 H), 2.34 (q, J = 7.5 Hz, 8 H), 2.37 (s, 6 H), 4.95 (s, 8 H), 7.19 (s, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.13 (q'), 21.51 (q'), 27.58 (t'), 64.03 (t'), 129.85 (d'), 129.96 (s'), 140.92 (s'), 141.01 (s'), 173.89 (s'); exact mass *m/z* calcd for $C_{30}H_{38}O_8S_2$ 590.20081, found 590.20072.

Bis[2,6-diformyl-4-methylphenyl]disulfide (121).

118 **121**

PCC (948 mg, 4.40 mmol) was added to a stirred mixture of tetraol **118** (197.2 mg, 0.541 mmol) and molecular sieves (4 Å, 1 g) in CH_2Cl_2 (30 mL). Stirring was continued for 2 h, then the mixture was filtered through a pad (3 x 4 cm) of silica gel, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 75% CH_2Cl_2-hexane, gave tetra(aldehyde) **121** (134.5 mg, 69%) as a pure (^1H NMR, 300 MHz), yellow solid: FTIR (CH_2Cl_2 cast) 2877, 2856, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 6 H), 7.94 (s, 4 H), 10.25 (s, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.34 (q'), 134.78 (d'), 136.29 (s'), 138.08 (s'), 143.02 (s'), 189.21 (d'); exact mass *m/z* calcd for $C_9H_7O_2S$ (M^+-$C_9H_7O_2S$) 179.01668, found 179.01654.

Bis[[2,6-bis[*N*-4-(methoxybenzyl)-*N*-pentylamino]-methyl)]-4-methylphenyl]disulfide (123).



119 **123**

i-Pr_2NEt (0.29 mL, 1.68 mmol) and (*p*-methoxybenzyl)-(*n*-pentyl)amine (348 mg, 1.68 mmol) were added successively to a stirred solution of tetrabromide **119** (104.0 mg, 0.168 mmol) in DMF (7 mL). Stirring was continued for 2.5 h and then the mixture was diluted with EtOAc (50 mL). The solution was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexane, gave tetraamine **123** (170.2 mg, 90%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1511, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.0 Hz, 12 H), 1.09-1.25 (m, 16 H), 1.35 (tt, *J* = 7.0, 7.0 Hz, 8 H), 2.19 (t, *J* = 7.0 Hz, 8 H), 2.32 (s, 6 H), 3.28 (s, 8 H), 3.37-3.63 (br s, 8 H), 3.77 (s, 12 H), 6.80 (d, *J* = 8.5 Hz, 8 H), 7.16 (d, *J* = 8.5 Hz, 8 H), 7.32 (s, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.16 (q'), 21.77 (q'), 22.62 (t'), 26.56 (t'), 29.67 (t'), 53.38 (t'), 55.21 (q'), 56.33 (t'), 57.74 (t'), 113.45 (d'), 128.35 (d'), 129.79 (d'), 131.23 (s'), 132.16 (s'), 139.13 (s'), 144.58

(s'), 158.38 (s'); mass (FAB) *m/z* calcd for $C_{70}H_{98}N_4O_4S_2$ 1123.7, found 1123.7.

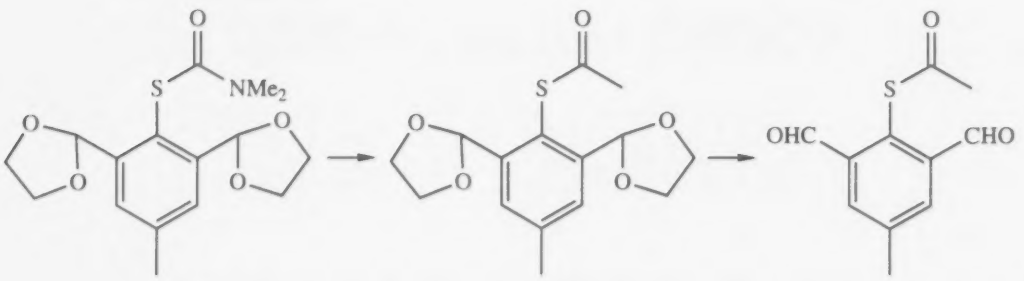
2-[*S*-(*N*,*N*-Dimethylthiocarbamoyl)]-5-methylisophthalaldehyde bis(ethylene acetal) (125).

116 **125**

Ethylene glycol (5.6 mL, 100 mmol) and PTSA (20.9 mg, 0.110 mmol) were added to a warmed (60 °C) and stirred solution of dialdehyde **116** (287.3 mg, 1.14 mmol) in PhH (40 mL). The oil bath temperature was increased to 115 °C and the mixture was refluxed, for 2.5 h through a Soxhlet apparatus containing a thimble filled with CaH_2. The mixture was cooled, diluted with EtOAc (70 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 70% EtOAc-hexane, gave diacetal **125** (337.5 mg, 87%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1672, 1113 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 2.42 (s, 3 H), 2.99 (s, 3 H), 3.12 (s, 3 H), 3.96-4.07 (m, 8 H), 6.17 (s, 2 H), 7.52 (s, 2 H); ^{13}C NMR (75.5 MHz CD_2Cl_2) δ 21.68 (q'), 37.20 (q'), 65.83 (t'), 101.76 (d'), 124.73 (s'),

128.89 (d'), 140.94 (s'), 142.52 (s'), 165.54 (s'); exact mass *m/z* calcd for $C_{16}H_{20}NO_5S$ (M^+-H) 338.10623; found 338.10590.

***S*-(Acetyl)-2-mercapto-5-methylisophthalaldehyde (126).**



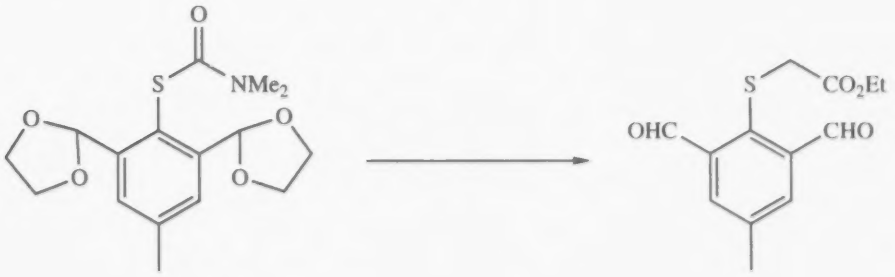
125 **125b** **126**

Aqueous NaOH (3 M, 5 mL) was added to a warmed (60 °C) solution of thionocarbamate **125** (331.4 mg, 0.976 mmol) in MeOH (20 mL). Stirring was continued for 12 h, and then the solution was cooled. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and the solution was adjusted to pH 4, using aqueous HCl (1 M). The product was extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in acetone (15 mL) and then Ac_2O (0.92 mL, 9.76 mmol) and K_2CO_3 (489 mg, 488 mmol) were added. The mixture was stirred for 1 h, diluted with EtOAc (200 mL), washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 30% EtOAc-hexane, gave thioester **125b** containing trace impurities (^1H NMR, 300 MHz).

Thioester **125b** was dissolved in acetone-water (10 mL:1 mL), and then PPTS (50 mg, 0.20 mmol) was added. The mixture was refluxed for 12 h, cooled, diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 20% EtOAc-hexane, gave dialdehyde **126** (50.0 mg, 23%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 2865, 1724, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3 H), 2.58 (s, 3 H), 8.07 (s, 2 H), 10.40 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_2$) δ 21.16 (q'), 30.55 (q'), 130.36 (s'), 134.65 (d'), 137.50 (s'), 141.56 (s'), 189.84 (d'), 191.46 (s'); exact mass *m/z* calcd for $C_{11}H_{10}O_3S$ 222.03506, found 222.03515.

_S_-[(Ethoxycarbonyl)methyl]-2-mercapto-5-methylisophthalaldehyde (128).



125 **128**

Aqueous NaOH (3M, 2 mL) was added to a warmed (60 °C) and stirred solution of thionocarbamate **125** (225.3 mg, 0.664 mmol) in MeOH (10 mL). Stirring was continued for 12 h and then the solution was cooled to room temperature. The

reaction was quenched with saturated aqueous NH_4Cl (30 mL) and the solution was adjusted to pH 4, using aqueous HCl (1 M). The solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in acetone (10 mL), and ethyl bromoacetate (0.74 mL, 6.64 mmol) and K_2CO_3 (332 mg, 3.32 mmol) were added. Stirring was continued for 30 min, and then the mixture was diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in acetone-water (10 mL:2 mL) and then PPTS (167 mg, 0.664 mmol) was added. The mixture was refluxed for 12 h, cooled, diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 20% EtOAc-hexane, gave dialdehyde **128** (80.0 mg, 45%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 2914, 2887, 1720, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3 H), 2.45 (s, 3 H), 3.47 (s, 2 H), 4.00 (q, J = 7.5 Hz, 2 H), 7.97 (s, 2 H), 10.80 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.97 (q'), 21.13 (q'), 40.27 (t'), 61.90 (t'), 134.58 (d'), 136.47 (s'), 138.72 (s'), 141.10 (s'), 168.27 (s'), 191.45 (s'); exact mass m/z calcd for $C_{13}H_{14}O_4S$ 266.06128, found 266.06101.

***S*-[2-(Trimethylsilyl)ethoxymethyl]-2-mercapto-4-methylisophthalaldehyde (130).**

SEM = $CH_2OCH_2CH_2SiMe_3$

125 **130**

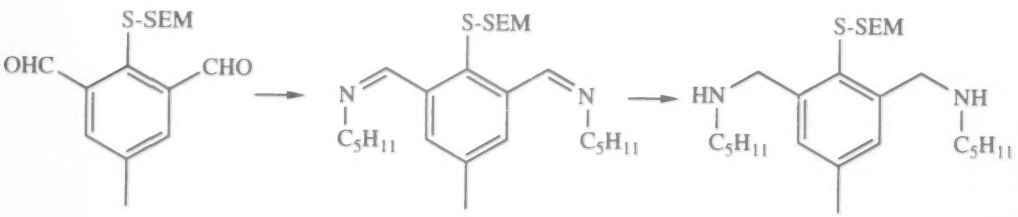
Aqueous NaOH (3 M, 5 mL) was added to a warmed (60 °C) and stirred solution of thionocarbamate **125** (318.6 mg, 0.939 mmol) in MeOH (20 mL). Stirring was continued for 12 h and then the solution was cooled to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the solution was adjusted to pH 4, using aqueous HCl (1 M). The solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in CH_2Cl_2 (10 mL), and then *i*-Pr_2NEt (0.37 mL, 2.10 mmol) and SEM-Cl (0.35 mL, 2.00 mL) were added. The mixture was stirred for 1 h, diluted with CH_2Cl_2 (80 mL), washed with water and brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in acetone-water (10 mL:2 mL) and then PPTS (50.2 mg, 0.200 mmol) was added. The mixture was refluxed for 12 h, cooled, diluted with EtOAc (70 mL),

washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexane, gave dialdehyde **130** (200.3 mg 68%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 2889, 2864, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 0.85-0.94 (m, 2 H), 2.49 (s, 3 H), 3.60-3.69 (m, 2 H), 4.78 (s, 2 H), 8.01 (s, 2 H), 10.75 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -1.47 (q'), 17.59 (t'), 21.07 (q'), 67.67 (t'), 79.04 (t'), 134.25 (d'), 138.28 (s'), 138.90 (s'), 140.31 (s'), 191.81 (d'); exact mass *m/z* calcd for $C_{14}H_{20}O_2SSi$ (M-CH_2O) 280.09534, found 280.09572.

2,6-Bis[(*N*-pentylamino)methyl]-4-methylphenyl 2-(trimethylsilyl)ethoxymethyl sulfide (132).



130 **131** **132**

n-$C_5H_{11}NH_2$ (0.23 mL, 2.00 mmol) was added to a stirred mixture of dialdehyde **130** (135.2 mg, 0.435 mmol) and molecular sieves (4 Å, 1 g) in PhH (6 mL). Stirring was continued for 8 h and then the mixture was filtered through a pad (1.5 x 2.5 cm) of Celite, using PhH as a rinse. The filtrate was evaporated, to give diimine **131** (191.6 mg, 98%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2

cast) 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.82-0.89 (m, 2 H), 0.92 (t, *J* = 6.0 Hz, 6 H), 1.32-1.41 (m, 8 H), 1.67-1.78 (m, 4 H), 2.40 (s, 3 H), 3.52-3.60 (m, 2 H), 3.65 (td, *J* = 7.0, 1.0 Hz, 4 H), 4.71 (s, 2 H), 7.90 (s, 2 H), 9.02 (t, *J* = 1.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -1.44 (q'), 14.08 (q'), 17.77 (t'), 21.05 (q'), 22.53 (t'), 29.63 (t'), 30.69 (t'), 61.98 (t'), 67.27 (t'), 78.86 (t'), 130.34 (d'), 132.25 (s'), 139.43 (s'), 139.53 (s'), 160.29 (s'); exact mass *m/z* calcd for $C_{19}H_{29}SN_2$ (M^+-$C_6H_{15}OSi$) 317.20514, found 317.20534.

$NaBH_4$ (68.1 mg, 180 mmol) was added to a stirred solution of diimine **131** (from previous experiment) in MeOH (6 mL). Stirring was continued for 1 h and then the reaction was quenched with water (0.5 mL). The resulting mixture was diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated, to give diamine **132** (191.1 mg, 97% from dialdehyde **130**) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3315 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.85-0.96 (m, 8 H), 1.27-1.36 (m, 8 H), 1.54 (tt, *J* = 7.0, 7.0 Hz, 4 H), 2.07-2.77 (br s, 2 H), 2.43 (s, 3 H), 2.64 (t, *J* = 7.0 Hz, 4 H), 3.56-3.64 (m, 2 H), 3.97 (s, 4 H), 4.78 (s, 2 H), 7.16 (s, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -1.46 (q'), 14.06 (q'), 17.91 (t'), 21.18 (q'), 22.61 (t'), 29.60 (t'), 29.64 (t'), 49.61 (t'), 53.02 (t'), 67.46 (t'), 78.11 (t'), 129.34 (s'), 130.00 (d'), 139.19 (s'), 144.51 (s'); exact mass *m/z* calcd for $C_{25}H_{48}N_2OSSi$ 452.32414; found 452.32565.

2-[(1,1-Dimethylethyl)thio]benzaldehyde (135).

134 **135**

o-Nitrobenzaldehyde (**134**; 4.00 g, 26.5 mmol) was converted into thioether **135** (4.67 g, 91%), using the procedure of Meth-Cohn and Tarnowski.[33] FTIR and ^{1}H NMR were the same as the reported data; compound **135** also has: ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.00 (q'), 47.59 (s'), 128.17 (d'), 129.59 (d'), 133.57 (d'), 136.73 (s'), 139.59 (s'), 140.02 (d'), 193.68 (d'); exact mass *m/z* calcd for $C_{11}H_{14}OS$ 194.07654, found 194.07647.

***N*-[2-[(1,1-Dimethylethyl)thio]benzylidene]pentylamine (136).**

135 **136**

n-$C_5H_{11}NH_2$ (1.39 mL, 12.0 mmol) was added to a stirred mixture of aldehyde **135** (1.80 g, 9.26 mmol) and molecular sieves (4 Å, 3 g) in PhH (40 mL). Stirring was continued for 6 h and then the mixture was filtered through a pad (2 x 3 cm) of Celite, using PhH as a rinse. The filtrate was

evaporated, to give imine **136** (2.39 g, 98%), as a pure (^{1}H NMR, 300 MHz), golden liquid: FTIR (CH_2Cl_2 cast) 1636 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.0 Hz, 3 H), 1.27 (s, 9 H), 1.32-1.41 (m, 4 H), 1.70 (tt, *J* = 7.0, 7.0 Hz, 2 H), 3.64 (td, *J* = 7.0, 1.5 Hz, 2 H), 7.33-7.45 (m, 2 H), 7.53-7.57 (m, 1 H), 8.08 (dd, *J* = 8.0, 2.0 Hz, 1 H), 9.06 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.08 (q'), 22.55 (t'), 29.66 (t'), 30.66 (t'), 31.08 (q'), 47.45 (s'), 61.75 (t'), 127.52 (d'), 129.43 (d'), 129.91 (d'), 133.31 (s'), 139.49 (d'), 140.85 (s'), 161.19 (d'); exact mass *m/z* calcd for $C_{12}H_{16}NS$ (M^+-^{t}Bu) 206.10034, found 206.09946.

N-[2-[(1,1-Dimethylethyl)thio]benzyl]pentylamine (137).

136 **137**

$NaBH_4$ (94.6 mg, 2.50 mmol) was added to a stirred solution of imine **136** (329.4 mg, 1.25 mmol) in MeOH (10 mL). Stirring was continued for 30 min and then the mixture was diluted with EtOAc (100 mL). The solution was washed with water and brine, dried ($MgSO_4$), and evaporated to give amine **137** (314.2 mg, 94%) as a pure (^{1}H NMR, 300 MHz), golden oil: FTIR (CH_2Cl_2 cast) 3340 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.25-1.35 (m, 13 H), 1.50 (tt, *J* = 7.0,

7.0 Hz, 2 H), 1.54-1.60 (br s, 1 H), 2.58 (t, J = 7.0 Hz, 2 H), 4.01 (s, 2 H), 7.21 (ddd, J = 7.5, 7.5, 2.0 Hz, 1 H), 7.32 (ddd, J = 7.5, 7.5, 2.0 Hz, 1 H), 7.44 (dd, J = 7.5, 2.0 Hz, 1 H), 7.54 (dd, J = 7.5, 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.08 (q'), 22.64 (t'), 29.60 (t'), 29.89 (t'), 31.21 (q'), 47.29 (s'), 49.28 (t'), 52.78 (t'), 126.84 (d'), 129.01 (d'), 129.64 (d'), 131.92 (s'), 138.90 (d'), 145.61 (s'); exact mass m/z calcd for $C_{16}H_{27}SN$ 265.18643, found 265.18561.

_N_-[2-[(1,1-Dimethylethyl)thio]benzyl]-_N_-pentylammonium chloride (138).

136 **138**

Na (575 mg, 25.0 mmol) was added over *ca.* 5 min to a cooled (-78 °C) and stirred mixture of imine **136** (1.341 g, 5.09 mmol) in NH_3 (40 mL). The cold bath was removed, stirring was continued for 15 min, and then the cold bath was replaced. NH_4Cl (1.50 g, 28.0 mmol) was added and the cold bath was again removed. After the NH_3 had evaporated, the residue was acidified to pH 1, using aqueous HCl (1 M). The mixture was diluted with water (100 mL), and the product was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from acetone to

give HCl-salt **138** (853.8 mg, 68%) as a pure (^{1}H NMR, 400 MHz), white solid: FTIR (CH_2Cl_2 cast) 2792, 2720, 2584 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.89 (t, *J* = 7.0 Hz, 3 H), 1.24-1.35 (m, 4 H), 1.73-1.83 (m, 2 H), 2.82 (t, *J* = 8.0 Hz, 2 H), 4.14 (s, 2 H), 4.54-4.80 (br s, 1 H), 7.23-7.32 (m, 2 H), 7.51 (dd, *J* = 7.0, 2.0 Hz, 1 H), 7.68 (dd, *J* = 7.0, 2.0 Hz, 1 H), 9.60-10.00 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.01 (q'), 22.43 (t'), 25.64 (t'), 29.19 (t'), 47.20 (t'), 49.19 (t'), 128.15 (d'), 130.38 (d'), 131.61 (s'), 132.49 (s'), 132.84 (s'), 134.91 (d'); mass (FAB) *m/z* calcd for $C_{12}H_{20}NS$ (M^+-Cl) 210.4, found 210.1.

Bis[2-[(*N*-pentylamino)methyl]phenyl]disulfide dihydrochloride (139).

138 **139**

O_2 was bubbled for 48 h through a stirred solution of thiophenol **138** (152.4 mg, 0.620 mmol) in aqueous NaOH (1 M, 9 mL). The mixture was acidified to pH 1, using aqueous HCl (1 M), and the product was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was crystallized from acetone to give disulfide **139** (82.6 mg, 54%) as a white solid containing trace impurities (^{1}H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 2870,

2858 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.89 (t, *J* = 6.0 Hz, 6 H), 1.23-1.33 (m, 8 H), 1.76 (tt, *J* = 7.5, 7.5 Hz, 4 H), 2.72 (t, *J* = 7.5 Hz, 4 H), 4.05 (s, 4 H), 7.31 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 2 H); 7.41 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 2 H), 7.49 (dd, *J* = 7.5, 1.5 Hz, 2 H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 2 H), 9.60-10.00 (br s, 4 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 14.05 (q'), 22.49 (t'), 25.73 (t'), 29.20 (t'), 47.47 (t'), 48.00 (t'), 130.45 (d'), 130.62 (d'), 132.15 (d'), 133.92 (s'), 135.37 (d'), 136.89 (s'); mass (FAB) *m/z* calcd for $C_{24}H_{38}N_2S_2$ (M^+-2Cl) 418.7, found 418.4.

2-Nitroisophthalic acid (141).

140 **141**

The literature procedure[35] was modified. $KMnO_4$ (122.3 g, 774 mmol) was added to a stirred suspension of xylene **140** (27.80 g, 184 mmol) in water (800 mL). The mixture was refluxed for 12 h and then the hot solution was filtered. The filter cake was washed with hot water (200 mL) and the combined filtrates were evaporated to a volume of *ca.* 250 mL. This solution was acidified to pH 1, using concentrated HCl, and the precipitate was collected. The solid was recrystallized from a mixture of $CHCl_3$, MeOH and hexane to give diacid **141** (22.40 g, 54%) as a pure (^1H NMR, 300 MHz),

white solid: FTIR (acetone cast) 1722, 1561, 1414, 1272 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.87 (t, *J* = 8.0 Hz, 1 H), 8.31 (d, *J* = 8.0 Hz, 2 H), 10.40-13.10 (br s, 2 H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 125.37 (s'), 131.63 (d'), 135.89 (d'), 150.57 (s'), 164.17 (s'); exact mass *m/z* calcd for $C_8H_5NO_6$ 211.01169, found 211.01191.

2,6-Bis(hydroxymethyl)nitrobenzene (142).

141 **142**

Diacid **29** (5.34 g, 25.3 mmol) was reduced to diol **30** (4.31 g, 93%), using BH_3:THF, as previously reported by Pavia *et al.*[36] FTIR and ^1H NMR data were the same as the literature data, and compound **142** also had: ^{13}C NMR (126 Hz, acetone-d_6) δ 60.11 (t'), 128.31 (d'), 131.57 (d'), 135.30 (s'), 148.67 (s'); exact mass *m/z* calcd for $C_8H_7NO_3$ (M^+-H_2O) 165.04259, found 165.04260.

2-Nitroisophthalaldehyde (143).

142 **143**

Diol **142** (1.30 g, 7.08 mmol) was oxidized using PCC (4.31 g, 20.0 mmol) according to the procedure reported by Pavia *et al.*[36] Flash chromatography of the crude product over silica gel (3.5 x 20 cm), using 50% EtOAc-hexane, gave dialdehyde **143** (1.08 g, 85%) as a pure (^{1}H NMR, 300 MHz), white solid: FTIR (acetone cast) 1705, 1595, 1546, 1019 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.11 (t, J = 7.5 Hz, 1 H), 8.40 (d, J = 7.5 Hz, 2 H), 10.12 (s, 2 H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 128.71 (s'), 133.08 (d'), 137.70 (d'), 148.72 (s'), 188.40 (d'); exact mass m/z calcd for $C_8H_3NO_3$ (M^+-H_2O) 161.01129, found 161.01112.

2-[(1,1-Dimethylethyl)thio]isophthalaldehyde (144).

143 **144**

K_2CO_3 (1.73 g, 12.5 mmol) and 2-methyl-2-propanethiol (2.00 mL, 17.7 mmol) were added successively to a stirred solution of nitrobenzene **143** (496.9 mg, 2.77 mmol) in DMF (2 mL). The mixture was heated to 100 °C and stirred at this temperature for 24 h. The mixture was cooled, diluted with EtOAc (250 mL), washed successively with water (1 x 100 mL), aqueous NaOH (2% w/v, 2 x 100 mL), water (1 x 100 mL) and brine (1 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm),

using 10% EtOAc-hexane, gave sulfide **144** (402.0 mg, 65%) as a pure (^{1}H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 2866, 1694, 1677 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9 H), 7.67 (td, *J* = 7.5, 1.0 Hz, 1 H), 8.23 (d, *J* = 7.5 Hz, 2 H), 10.90 (d, *J* = 1.0 Hz, 2 H); ^{13}C NMR (75,5 MHz, $CDCl_3$) δ 30.95 (q'), 49.76 (s'), 129.89 (d'), 133.34 (d'), 139.64 (s'), 140.85 (s'), 192.36 (d'); exact mass *m/z* calcd for $C_{12}H_{14}O_2S$ 222.07146, found 222.07118.

2,6-Bis(*N*-methylidene-*N*-pentylamino)(1,1-dimethylethyl)thiobenzene (145).

144 **145**

n-$C_5H_{11}NH_2$ (0.93 mL, 8.0 mmol) was added to a stirred mixture of dialdehyde **144** (448.6 mg, 2.02 mmol) and molecular sieves (4 Å, 2 g) in PhH (20 mL). Stirring was continued for 5 h and then the mixture was filtered through a pad of (2 x 3 cm) Celite, using PhH as a rinse. The filtrate was evaporated, to give diimine **145** (713.8 mg, 98%) as a pure (^{1}H NMR, 300 MHz), colorless liquid: FTIR (CH_2Cl_2 cast) 1632 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.0 Hz, 6 H), 1.22 (s, 9 H), 1.32-1.41 (m, 8 H), 1.66-1.76 (m, 4 H), 3.66 (td, *J* = 7.0, 1.0 Hz, 4 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 8.14 (d, *J* = 7.5 Hz, 2 H), 9.16 (d, *J* = 1.0 Hz, 2 H); ^{13}C NMR (75.5

MHz, $CDCl_3$) δ 14.07 (q'), 22.55 (t'), 29.71 (t'), 30.62 (t'), 31.27 (q'), 49.57 (s'), 61.74 (t'), 129.45 (d'), 129.52 (d'), 133.84 (s'), 141.92 (s'), 161.31 (d'); exact mass *m/z* calcd for $C_{22}H_{35}SN_2$ (M^+-H) 359.25211, found 359.25400.

2,6-Bis[(*N*-pentylamino)methyl](1,1-dimethylethyl)-thiobenzene (146).

145 **146**

$NaBH_4$ (75.7 mg, 2.00 mmol) was added to a stirred solution of diimine **145** (153.1 mg, 0.424 mmol) in MeOH (10 mL). Stirring was continued for 30 min and then the mixture was diluted with EtOAc (75 mL). The solution was washed with water and brine, dried ($MgSO_4$), and evaporated, to give diamine **146** (146.4 mg, 94%) as a pure (^1H NMR, 300 MHz), golden oil: FTIR (CH_2Cl_2 cast) 3335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 6 H), 1.24-1.34 (m, 17 H), 1.49 (tt, *J* = 7.0, 7.0 Hz, 4 H), 1.66-1.76 (br s, 2 H), 2.55 (t, *J* = 7.0 Hz, 4 H), 3.50-4.50 (br s, 4 H), 7.26-7.39 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.06 (q'), 22.61 (t'), 29.58 (t'), 29.85 (t'), 31.57 (q'), 49.03 (s'), 49.24 (t'), 53.33 (t'), 128.41 (d'), 129.09 (d'), 131.02 (s'), 147.07 (s'); exact mass *m/z* calcd for $C_{22}H_{40}N_2S$ 364.29123, found 364.29.091.

8-Chloromethyl-1-naphthoyl chloride (155).

154 **155**

Lactone **154**[38] (1.26 g, 6.84 mmol) was converted into acid chloride **155** (1.30 g, 80%) using the method of Bahlmann and Kapp.[39] Compound **155** had: FTIR (CH_2Cl_2 cast) 1752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 2 H), 7.50-7.60 (m, 2 H), 7.73 (dd, *J* = 7.0, 1.0 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.05-8.12 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 47.96 (t'), 124.60 (d'), 126.13 (d'), 127.62 (s'), 128.80 (s'), 130.51 (d'), 130.58 (d'), 131.72 (d'), 133.43 (s'), 134.00 (d'), 136.16 (s'), 174.29 (s'); exact mass *m/z* calcd for $C_{12}H_8{}^{35}ClO$ (M^+-^{35}Cl) 203.02637, found 203.02622.

Methyl 8-Chloromethyl-1-naphthoate (156).

155 **156**

MeOH (5 mL) was added to a cooled (0 °C) and stirred solution of acid chloride **155** (1.24 g, 5.17 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 1 h and then the mixture was diluted with CH_2Cl_2 (200 mL). The solution was washed

with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 25% EtOAc-hexane, gave ester **156** (955 mg, 79%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1717, 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3 H), 5.16 (s, 2 H), 7.46-7.55 (m, 2 H), 7.65 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.83 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.89 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.00 (dd, *J* = 7.0, 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 47.68 (t'), 53.06 (q'), 124.59 (d'), 125.88 (d'), 127.42 (s'), 129.42 (s'), 130.15 (s'), 130.66 (d'), 131.09 (d'), 132.93 (d'), 133.24 (s'), 135.10 (s'), 170.96 (s'); exact mass *m/z* calcd for $C_{13}H_{11}{}^{35}ClO_2$ 234.04475, found 234.04353.

8-Chloromethyl-1-naphthaldehyde (157).

156 **157**

DIBAL (1 M in CH_2Cl_2, 8.7 mL, 8.7 mmol) was added dropwise over *ca.* 10 min to a cooled (0 °C) and stirred solution of ester **156** (925 mg, 3.94 mmol) in CH_2Cl_2 (20 mL). The mixture was warmed to room temperature, stirred for 1 h, diluted with CH_2Cl_2 (200 mL), washed with aqueous HCl (1 M) and brine, dried ($MgSO_4$), and evaporated.

The residue was dissolved in CH_2Cl_2 (20 mL), and then molecular sieves (4 Å, 3 g) and PCC (1.08 g, 5.00 mmol) were added successively. The mixture was stirred for 1 h and then filtered through a pad (3 x 3 cm) of silica gel, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 20% EtOAc-hexane, gave aldehyde **157** (605 mg, 75%) as a pure (^{1}H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 2861, 1679 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 2 H), 7.50-7.78 (m, 3 H), 7.89-7.46 (m, 3 H), 10.70 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 48.22 (t'), 124.88 (d'), 126.34 (d'), 128.16 (s'), 130.73 (d'), 131.93 (d'), 132.04 (d'), 133.56 (s'), 135.23 (s'), 135.37 (d'), 135.63 (s'), 193.02 (d'); exact mass *m/z* calcd for $C_{12}H_9{}^{35}ClO$ 204.03419, found 204.03393.

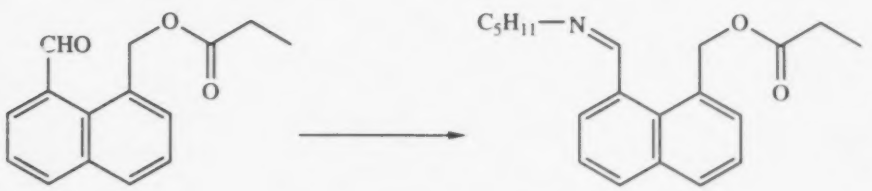
8-[(Propionyloxy)methyl]-1-naphthaldehyde (158).

157 **158**

LiI (201 mg, 1.50 mmol) was added to a stirred solution of chloride **157** (271.4 mg, 1.33 mmol) in DMF (10 mL). Stirring was continued for 30 min, cesium propionate (412 mg, 2.00 mmol) was added, and stirring was continued for a further 6 h. The mixture was diluted with EtOAc (100 mL), washed with water and brine, dried ($MgSO_4$), and evaporated.

Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 15% EtOAc-hexane, gave propionate **158** (286.4, 89%) as a pure (^{1}H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1738, 1687, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3 H), 2.33 (q, J = 7.5 Hz, 2 H), 5.54 (s, 2 H), 7.50-7.63 (m, 2 H), 7.72 (dd, J = 7.0, 1.5 Hz, 1 H), 7.92 (dd, J = 8.0, 1.5 Hz, 1 H), 8.01 (dd, J = 7.0, 1.5 Hz, 1 H), 8.09 (dd, J = 8.0, 1.5 Hz, 1 H), 10.63 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.96 (q'), 27.64 (t'), 67.11 (t'), 124.90 (d'), 126.19 (d'), 129.14 (s'), 130.38 (d'), 131.16 (d'), 131.31 (d'), 131.74 (s'), 134.97 (s'), 135.22 (d'), 135.39 (s'), 173.86 (s'), 193.06 (d'); exact mass m/z calcd for $C_{15}H_{14}O_3$ 242.09430, found 242.09478.

_N_-1-[8-[(Propionyloxy)methyl]naphthylidene]pentylamine (159).

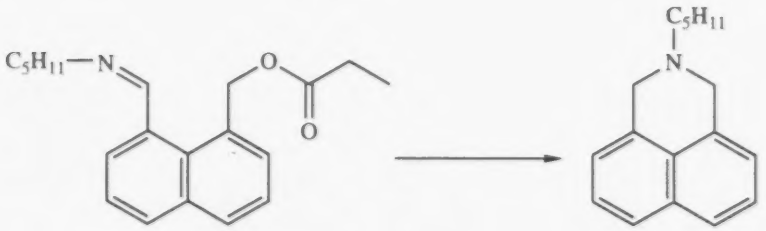


158 **159**

n-$C_5H_{11}NH_2$ (0.12 mL, 1.0 mmol) was added to a stirred mixture of aldehyde **158** (200.3 mg, 0.827 mmol) and molecular sieves (4 Å, 2 g) in PhH (10 mL). Stirring was continued for 4 h and then the mixture was filtered through a pad (2 x 3 cm) of Celite, using PhH as a rinse. The filtrate was evaporated to give imine **159** (246.5 mg, 96%) as a pure (^{1}H

NMR, 300 MHz), golden oil: FTIR (CH_2Cl_2 cast) δ 1738, 1637, 1174 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.94 (t *J* = 7.0 Hz, 3 H), 1.15 (t, *J* = 7.5 Hz, 3 H), 1.35-1.46 (m, 4 H), 1.75 (tt, *J* = 7.0, 7.0 Hz, 2 H), 2.39 (q, *J* = 7.5 Hz, 2 H), 3.64 (td, *J* = 7.0, 1.5 Hz, 2 H), 5.44 (s, 2 H), 7.46-7.57 (m, 2 H), 7.64 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.82 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.90-7.98 (m, 2 H), 9.01 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 9.28 (q'), 14.24 (q'), 22.96 (t'), 28.04 (t'), 30.14 (t'), 30.90 (t'), 62.40 (t'), 66.99 (t'), 125.71 (d', d' overlapping), 129.14 (d'), 130.44 (s'), 130.80 (d'), 131.26 (d'), 131.44 (d'), 131.95 (s'), 135.17 (s'), 135.20 (s'), 162.64 (d'), 174.10 (s'); exact mass *m/z* calcd for $C_{20}H_{25}NO_2$ 311.18854, found 311.18723.

2,3-Dihydro-*N*-pentyl-1*H*-benz[de]isoquinoline (160).

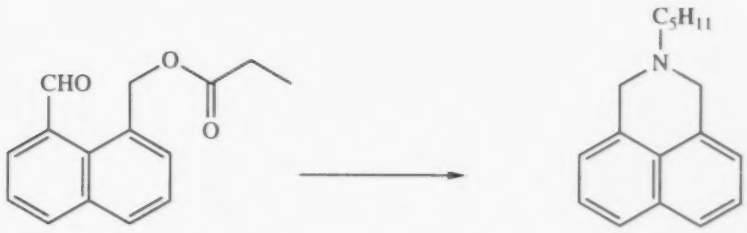


159 **160**

$NaBH_4$ (45.4 mg, 1.20 mmol) was added to a stirred solution of imine **159** (199.8 mg, 0.642 mmol) in MeOH (10 mL). Stirring was continued for 10 h and then the mixture was diluted with EtOAc (75 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 15% EtOAc-

hexane, gave tertiary amine **160** (104.7 mg, 68%) as a pure (^{1}H NMR, 300 MHz), golden oil: FTIR (CH_2Cl_2 cast) 2930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.0 Hz, 3 H), 1.30-1.43 (m, 4 H), 1.62-1.74 (m, 2 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 3.97 (s, 4 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.39 (dd, *J* = 7.5, 7.5 Hz, 2 H), 7.69 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.09 (q'), 22.70 (t'), 27.13 (t'), 29.85 (t'), 56.96 (t'), 57.89 (t'), 122.02 (d'), 125.62 (d'), 126.07 (d'), 128.31 (s'), 133.18 (s'), 133.59 (s'); exact mass *m/z* calcd for $C_{17}H_{21}N$ 239.16740, found 239.16770.

2,3-Dihydro-*N*-pentyl-1*H*-benz[de]isoquinoline (160) from aldehyde 158.



158 **160**

n-$C_5H_{11}NH_2$ (31 μL, 0.27 mmol) and $NaBH_3CN$ (31.4 mg, 0.500 mmol) were added successively to a stirred solution of aldehyde **158** (58.6 mg, 0.242 mmol) in PhH (3 mL) and MeOH (1 mL). Stirring was continued for 6 h and then the mixture was diluted with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 15% EtOAc-hexane, gave tertiary amine **160** (29.2 mg, 50%) as a golden

oil containing trace impurities (^{1}H NMR, 300 MHz). This product was spectroscopically identical (apart from the trace impurities) with the product obtained in the preceding experiment.

8-Hydroxy-1-naphthaldehyde (162).

161 **162**

Lactone **161** (16.7 g, 98.1 mmol) was converted into aldehyde **162** (9.43 g, 56%) using the method of Elliger.[40] Compound **162** had: FTIR (CH_2Cl_2 cast) 3059, 2863, 2813, 1657 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.14 (dd, J = 7.5, 1.5 Hz, 1 H), 7.42-7.64 (m, 3 H), 8.08 (dd, J = 7.0, 1.5 Hz, 1 H), 8.17 (dd, J = 8.0, 1.5 Hz, 1 H), 9.87 (d, J = 1.0 Hz, 1 H), 11.63 (d, J = 1.0 Hz, 1 H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 116.01 (d'), 120.77 (d'), 121.45 (s'), 124.80 (d'), 129.30 (d'), 132.77 (s'), 136.72 (s'), 139.39 (d'), 143.47 (d'), 155.58 (s'), 198.55 (d'); exact mass *m/z* calcd for $C_{11}H_8O_2$ 172.05243, found 172.05210.

1-(8-Formylnaphthyl) propionate (163).

162 **163**

A solution of naphthol **162** (332 mg, 1.86 mmol) in Et_2O (8 mL plus 3 mL as a rinse) was added to a cooled (0 °C) and stirred suspension of NaH (72.0 mg, 3.00 mmol) in Et_2O (10 mL). Stirring was continued for 30 min and then a solution of EtCOCl (555 mg, 6.00 mmol) in Et_2O (8 mL plus 3 mL as a rinse) was added. The cold bath was removed, stirring was continued for 15 min, and then the mixture was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 10% EtOAc-hexane, gave ester **163** (367 mg, 86%) as a pure (^1H NMR, 300 MHz), white solid: FTIR (CH_2Cl_2 cast) 1766, 1684, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 2.71 (q, J = 7.5 Hz, 2 H), 7.41 (dd, J = 8.0, 1.5 Hz, 1 H), 7.53-7.61 (m, 2 H), 7.83 (dd, J = 8.0, 1.5 Hz, 1 H), 7.98 (dd, J = 8.0, 1.5 Hz, 1 H), 8.06 (dd, J = 8.0, 1.5 Hz, 1 H), 10.90 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 8.87 (q'), 28.13 (t'), 121.61 (d'), 124.89 (s'), 125.65 (d'), 126.28 (d'), 126.94 (d'), 129.12 (d'), 133.66 (s'), 133.85 (d'), 135.57 (s'), 146.42

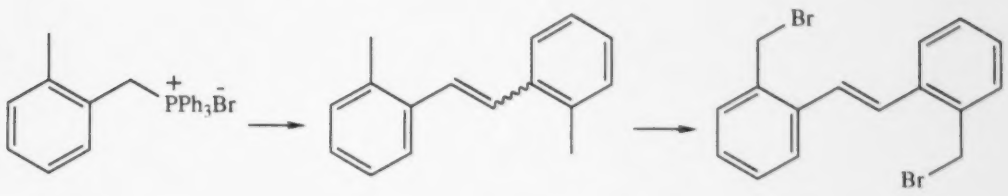
(s'), 172.45 (s') 193.21 (d'); exact mass *m/z* calcd for $C_{14}H_{12}O_3$ 228.07864, found 228.07852.

***N*-[1-(8-Hydroxynaphthyl)methylidene]pentylamine (165).**

162 **165**

n-$C_5H_{11}NH_2$ (0.12 mL, 1.0 mmol) was added to a stirred mixture of aldehyde **162** (88.1 mg, 0.521 mmol) and molecular sieves (4 Å, 2 g) in PhH (10 mL). Stirring was continued for 2 h and then the mixture was filtered through a pad (2 x 3 cm) of Celite, using PhH as a rinse. The filtrate was evaporated to give imine **165** (119.0 mg, 96%) as a pure (^{1}H NMR, 300 MHz), golden oil: FTIR (CH_2Cl_2 cast) 3397, 1650 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.93 (t, *J* = 7.0 Hz, 3 H), 1.34-1.48 (m, 4 H), 1.78 (tt, *J* = 7.0, 7.0 Hz, 2 H), 3.69 (td, *J* = 7.0, 1.0 Hz, 2 H), 6.94 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.30 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.37-7.44 (m, 2 H), 7.60 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.90 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.34 (t, *J* = 1.0 Hz, 1 H), 11.46 (s, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.14 (q'), 22.80 (t'), 29.72 (t'), 30.41 (t'), 59.54 (t'), 114.75 (d'), 119.42 (d'), 122.89 (s'), 124.59 (d'), 128.70 (d'), 132.16 (s'), 134.87 (d'), 136.60 (d'), 137.45 (s'),157.63 (s'), 167.66 (d'); exact mass *m/z* calcd for $C_{16}H_{19}NO$ 241.14667, found 241.14686.

(Z)-2,2'-Bis(bromomethyl)stilbene (168).



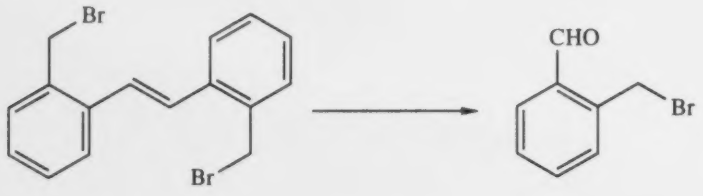
166 **167** **168**

NaH (540 mg, 22.5 mmol) was added to a stirred suspension of phosphonium salt **166** in THF (100 mL). The mixture was refluxed for 4 h and then a solution of *o*-tolualdehyde (3.00 g, 25.0 mmol) in THF (15 mL plus 5 mL as a rinse) was added. The resulting mixture was refluxed for 2.5 h, cooled to room temperature, and then evaporated. The residue was stirred in hexane (200 mL) and the insoluble Ph_3PO was filtered off. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3.5 x 20 cm), using hexane, gave olefin **167** (3.53 g, 84%) as a mixture (^1H NMR, 300 MHz) of stereoisomers.

The reaction mixture was dissolved in CCl_4 (200 mL) and then NBS (6.41 g, 36.0 mmol) was added. The mixture was refluxed for 12 h, using a 300 W tungsten light bulb as a heat source. The mixture was cooled and filtered through a pad (4 x 6 cm) of Celite, using CCl_4 as a rinse. The filtrate was evaporated and the residue was crystallized from a mixture of acetone and hexane to give dibromide **168** (3.64 g, 49% from compound **166**) as a pure (^1H NMR, 300 MHz), white solid: FTIR (microscope) 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 4 H), 7.25-7.42 (m, 6 H), 7.46 (s, 2 H), 7.70 (d, *J*

= 7.5 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 31.98 (t'), 126.88 (d'), 128.02 (d'), 128.31 (d'), 129.42 (d'), 130.52 (d'), 135.08 (s'), 136.95 (s'); exact mass calcd for $C_{16}H_{14}{}^{79}Br_2$ 363.94623, found 363.94531.

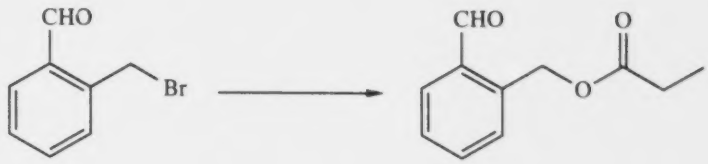
2-(Bromomethyl)benzaldehyde (169).



168 **169**

O_3 was bubbled through a cooled (-78 °C) and stirred solution of olefin **168** (3.14 g, 8.58 mmol) in CH_2Cl_2 (250 mL) until a blue color developed (*ca.* 30 min). O_2 was then bubbled through the solution for 10 min and Ph_3P (2.25 g, 8.58 mmol) was then added. The cold bath was removed and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 20 cm), using 10% EtOAc-hexane, gave aldehyde **169** (2.95 g, 80%) as a white solid containing trace impurities (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 2837, 2746, 1697 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 4.96 (s, 2 H), 7.46-7.64 (m, 3 H), 7.85 (dd, *J* = 7.5, 1.5 Hz, 1 H), 10.24 (s, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 30.08 (t'), 129.54 (d'), 132.03 (d'), 133.59 (s'), 134.06 (d'), 134.30 (d'), 139.54 (s'), 192.34 (d'); exact mass calcd for $C_8H_7{}^{79}BrO$ 197.96803, found 197.96822.

2-(1-Formylbenzyl) propionate (170).



169 **170**

Cesium propionate (206 mg, 1.00 mmol) was added to a stirred solution of bromide **169** (150.5 mg, 0.756 mmol) in DMF (5 mL). Stirring was continued for 1 h and the mixture was diluted with EtOAc (70 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexane, gave propionate **170** (131.5 mg, 90%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2882, 2840, 1741, 1696, 1194 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 7.5 Hz, 3 H), 2.43 (q, J = 7.5 Hz, 2 H), 5.56 (s, 2 H), 7.49-7.55 (m, 2 H), 7.61 (ddd, J = 7.0, 7.0, 1.5 Hz, 1 H), 7.88 (dd, J = 8.0, 1.5 Hz, 1 H), 10.20 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.13 (q'), 27.58 (t'), 63.37 (t'), 128.41 (d'), 128.64 (d'), 133.10 (d'), 133.65 (s'), 133.93 (d'), 138.10 (s'), 173.93 (s'), 192.36 (d'); exact mass *m/z* calcd for $C_8H_7O_2$ (M^+-C_3H_5O) 135.04460, found 135.04422.

_N_-[2-[(Propionyloxy)methyl]benzylidene]pentylamine (171).

170 **171**

n-$C_5H_{11}NH_2$ (70 μL, 0.60 mmol) was added to a stirred mixture of aldehyde **170** (55.9 mg, 0.291 mmol) and molecular sieves (4 Å, 1 g) in PhH (5 mL). Stirring was continued for 4 h and the mixture was filtered through a pad (2 x 3 cm) of Celite, using PhH as a rinse. The filtrate was evaporated to give imine **171** (71.1 mg, 93%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1741, 1644, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.0 Hz, 3 H), 1.16 (t, *J* = 7.5 Hz, 3 H), 1.30-1.40 (m, 4 H), 1.64-1.76 (m, 2 H), 2.38 (q, *J* = 7.5 Hz, 2 H), 3.63 (td, *J* = 7.0, 1.5 Hz, 2 H), 5.40 (s, 2 H), 7.35-7.46 (m, 3 H), 7.82-7.90 (m, 1 H), 8.53 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.15 (q'), 14.09 (q'), 22.54 (t'), 27.67 (t'), 29.60 (t'), 30.70 (t'), 62.32 (t'), 63.94 (t'), 128.49 (d'), 128.74 (d'), 129.28 (d'), 130.03 (d'), 134.65 (s'), 135.28 (s'), 158.87 (d'), 174.11 (s'); exact mass calcd for $C_{16}H_{23}NO_2$ 261.17288, found 261.17243.

N-[2-[(Propionyloxy)methyl]benzyl]pentylamine (172).

171 **172**

$NaBH_4$ (18.5 mg, 0.500 mmol) was added to a stirred solution of imine **171** (58.1 mg, 0.222 mmol) in MeOH (7 mL). Stirring was continued for 3 h and the mixture was diluted with EtOAc (70 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.0 x 10 cm), using 15% EtOAc-hexane, gave amide **172** (36.6 mg, 62%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1739, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.25-1.37 (m, 5 H), 1.50 (tt, J = 7.0, 7.0 Hz, 2 H), 2.37 (q, J = 7.5 Hz, 2 H), 2.64 (t, J = 7.0 Hz, 2 H), 3.82 (s, 2 H), 5.24 (s, 2 H), 7.22-7.40 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.14 (q'), 14.07 (q'), 22.65 (t'), 27.66 (t'), 29.61 (t'), 29.91 (t'), 49.91 (t'), 51.31 (t'), 64.03 (t'), 127.20 (d'), 128.51 (d'), 129.24 (d'), 129.66 (d') 134.29 (s'), 139.30 (s'), 174.20 (s'); exact mass calcd for $C_{13}H_{18}NO$ (M^+-C_3H_7O) 204.13884, found 204.13683.

***N*-(2-Hydroxybenzylidene)pentylamine (174).**

173 **174**

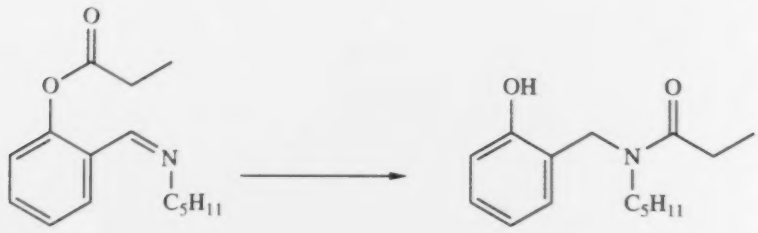
n-$C_5H_{11}NH_2$ (1.29 mL, 12.0 mmol) was added to a stirred mixture of benzaldehyde **173** (1.15 g, 9.38 mmol) and molecular sieves (4 Å, 1 g) in PhH (10 mL). Stirring was continued for 4 h and then the mixture was filtered through a pad (2 x 3 cm) of Celite, using PhH as a rinse. The filtrate was evaporated to give imine **174** (1.74 g, 97%) as a pure (^{1}H NMR, 300 MHz), golden oil: FTIR (CH_2Cl_2 cast) 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3 H), 1.32-1.42 (m, 4 H), 1.67-1.74 (m, 2 H), 3.59 (td, J = 7.0, 1.0 Hz, 2 H), 6.86 (ddd, J = 7.0, 7.0, 1.0 Hz, 1 H), 6.96 (dd, J = 8.0, 0.5 Hz, 1 H), 7.21-7.33 (m, 2 H), 8.33 (t, J = 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.02 (q'), 22.44 (t'), 29.39 (t'), 30.58 (t'), 59.56 (t'), 117.06 (d'), 118.38 (d'), 118.87 (s'), 131.06 (d'), 132.02 (d'), 161.44 (s'), 164.43 (d'); exact mass *m/z* calcd for $C_{12}H_{17}NO$ 191.13101, found 191.13064.

_N_-[2-(Propionyloxy)benzylidene]pentylamine (175).

174 **175**

Et_3N (1.4 mL, 10 mmol) and EtCOCl (0.43 mL, 5.0 mmol) were added successively to a stirred solution of phenol **174** in Et_2O (10 mL). Stirring was continued for 1 h and then hexane (5 mL) was added. The mixture was filtered through a pad (2 x 3 cm) of Celite, using 50% Et_2O-hexane as a rinse. Evaporation of the solvent gave propionate **175** (948.6 mg, 99%) as a golden oil containing trace impurities (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 1766, 1643, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.31-1.39 (m, 4 H), 1.63-1.74 (m, 2 H), 2.65 (q, J = 7.5 Hz, 2 H), 3.59 (td, J = 7.0, 1.0 Hz, 2 H), 7.08 (dd, J = 8.0, 1.0 Hz, 1 H), 7.24-7.31 (m, 1 H), 7.38-7.45 (m, 1 H), 7.91 (dd, J = 7.5, 2.0 Hz, 1 H), 8.32 (t, J = 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.07 (q'), 14.04 (q'), 22.51 (t'), 27.66 (t'), 29.51 (t'), 30.57 (t'), 62.37 (t'), 122.79 (d'), 126.10 (d'), 128.33 (s'), 128.77 (d'), 131.13 (d'), 149.89 (s'), 155.67 (d'), 172.73 (s'); exact mass *m/z* calcd for $C_{15}H_{21}NO_2$ 247.15723, found 247.15658.

***N*-2-Hydroxybenzyl-*N*-pentylpropanamide (176).**



175 **176**

$NaBH_4$ (148 mg, 4.00 mmol) was added to a stirred solution of imine **175** (491.4 mg, 1.99 mmol) in MeOH (20 mL). Stirring was continued for 30 min and then the mixture was diluted with EtOAc (200 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 15% EtOAc-hexane, gave amide **176** (392.8 mg, 79%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3167, 1619 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.25-1.43 (m, 4 H), 1.58-1.71 (m, 2 H), 2.37 (q, J = 7.5 Hz, 2 H), 3.27 (t, J = 8.0 Hz, 2 H), 4.43 (s, 2 H), 6.79 (ddd, J = 7.0, 7.0, 1.0 Hz, 1 H), 6.93 (dd, J = 7.0, 1.0 Hz, 1 H), 7.09 (dd, J = 7.0, 1.0 Hz, 1 H), 7.72 (ddd, J = 7.0, 7.0, 1.0 Hz, 1 H), 9.27 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.47 (q'), 13.95 (q'), 22.38 (t'), 26.10 (t'), 27.88 (t'), 29.03 (t'), 46.56 (t'), 47.59 (t'), 117.63 (d'), 119.08 (d'), 122.43 (s'), 130.19 (d'), 131.39 (d'), 156.47 (s'), 175.85 (s'); exact mass *m/z* calcd for $C_{15}H_{23}NO_2$ 249.17288, found 249.17222.

4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]butanal (181).

180 **181**

O_3 was bubbled through a cooled (-78 °C) and stirred solution of olefin **180** (2.12 g, 10.6 mmol) in CH_2Cl_2 (100 mL) until a blue color developed (*ca.* 20 min). O_2 was then bubbled through the solution of 10 min, and Ph_3P (2.78 g, 10.6 mmol) was then added. The cold bath was removed, stirring was continued for 3 h, and the solution was evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 5% EtOAc-hexane, gave aldehyde **181** (1.76 g, 82%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2886, 2857, 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.85 (tt, J = 7.0, 6.0 Hz, 2 H), 2.50 (td, J = 7.0, 2.0 Hz, 2 H), 3.65 (t, J = 6.0 Hz, 2 H), 9.79 (t, J = 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.37 (q'), 18.32 (s'), 25.56 (t'), 25.94 (q'), 40.82 (t'), 62.13 (t') 202.64 (d'); exact mass *m/z* calcd for $C_{10}H_{21}O_2Si$ (M^+-H) 201.13109, found 201.13110.

(±)-2-Bromo-4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]butanal (182).

181 **182**

Et_3N (2.8 mL, 20 mmol) and Me_3SiCl (1.3 mL, 10 mmol) were added successively to a stirred solution of aldehyde **181** (1.00 g, 4.94 mmol) in DMF (10 mL). The mixture was heated to 130 °C and stirring was continued for 40 h. The mixture was cooled, diluted with hexane (200 mL), washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated.

The residue was dissolved in CH_2Cl_2 (30 mL) and the solution was cooled (-78 °C). A solution of Br_2 (0.25 mL) in CH_2Cl_2 (5 mL) was added dropwise over *ca.* 15 min, and the mixture was warmed to room temperature, diluted with CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 5% EtOAc-hexane, gave α-bromoaldehyde **182** (1.01 g, 72%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2883, 2857, 1729 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.06 (d, J = 1.0 Hz, 6 H), 0.89 (s, 9 H), 2.02-2.15 (m, 1 H), 2.23-2.36 (m, 1 H), 3.71-3.86 (m, 2 H), 4.45-4.52 (m, 1 H), 9.45 (d, J = 2.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.43 (q'), 18.47 (s'), 25.97 (q'), 35.62 (t'), 53.67 (d'), 59.97 (t'), 193.16 (d'); exact mass

m/z calcd for $C_6H_{12}{}^{79}BrO_2Si$ ($M^+-C_4H_9$) 22.97899, found 222.97915.

(±)-2-(Propionyloxy)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butanal (183).

182 **183**

Cesium propionate (309 mg, 1.50 mmol) was added to a stirred solution of bromide **182** (267.6 mg, 0.951 mmol) in DMF (7 mL). Stirring was continued for 2 h and then the mixture was diluted with EtOAc (100 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 10% EtOAc-hexane, gave propionate **183** (232.2 mg, 89%) as a colorless oil containing trace impurities (^1H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 2884, 2858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.20 (t, *J* = 7.5 Hz, 3 H), 1.96-2.14 (m, 2 H), 2.46 (qd, *J* = 7.5, 2.5 Hz, 2 H), 3.65-3.82 (m, 2 H), 5.17 (t, *J* = 6.0 Hz, 1 H), 9.53 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.50 (q'), 9.08 (q'), 18.23 (s'), 25.86 (q'), 27.32 (t'), 32.45 (t'), 58.01 (t'), 75.45 (d'), 173.84 (s'), 198.07 (d'); exact mass *m/z* calcd for $C_{13}H_{25}O_4Si$ (M^+-H) 273.15222, found 273.15178.

(±)-*N*-[2-(Propionyloxy)-4-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]butylidene]pentylamine (184).

183 **184**

n-$C_5H_{11}NH_2$ (0.14 mL, 1.2 mmol) was added to a stirred mixture of aldehyde **183** (167.4 mg, 0.610 mmol) and molecular sieves (4 Å, 0.5 g) in PhH (7 mL). Stirring was continued for 4 h and then the mixture was filtered through a pad (2 x 3 cm) of Celite, using PhH as a rinse. The filtrate was evaporated to give imine **184** (1.98 mg, 93%) as a golden oil containing trace impurities (^{1}H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 1744, 1677, 1100 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.06 (s, 6 H), 0.80-0.94 (m, 12 H), 1.12 (t, *J* = 7.5 Hz, 3 H), 1.23-1.40 (m, 4 H), 1.55 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.81-2.07 (m, 2 H), 2.34 (q, *J* = 7.5 Hz, 2 H), 3.29-3.46 (m, 2 H), 3.70 (td, *J* = 7.0, 1.5 Hz, 2 H), 5.25-5.33 (m, 1 H), 7.57 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.38 (q'), 9.17 (q'), 14.03 (q'), 18.31 (s'), 22.45 (t'), 25.94 (q'), 27.61 (t'), 29.36 (t'), 30.24 (t'), 34.95 (t'), 58.88 (t'), 61.12 (t'), 71.69 (d'), 161.96 (d'), 173.74 (s'), exact mass *m/z* calcd for $C_{14}H_{28}NO_3Si$ (M^+-C_4H_9) 286.18384, found 286.18353.

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